

Association between Apparent Diffusion Coefficient Values on Diffusion Weighted Imaging and Prognostic Factors of Breast Cancer

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ABSTRACT

Objective: To evaluate the association between apparent diffusion coefficient (ADC) values and prognostic factors of breast cancer.

Methods: All patients with breast cancer who underwent breast magnetic resonance imaging and subsequent surgery in Kwong Wah Hospital from January 2012 to December 2016 were retrospectively reviewed. The ADC values of the malignant lesions were recorded and compared with tumour size (≥ 2 cm, < 2 cm), tumour grading (modified Bloom-Richardson-Elston grade 1, 2, 3), tumour aggressiveness (ductal in situ carcinoma and grade 1 invasive carcinomas, grade 2-3 invasive carcinomas), axillary lymph node status (positive, negative), oestrogen receptor expression (positive, negative), progesterone receptor expression (positive, negative), and human epidermal growth factor receptor 2 receptor status (positive, negative).

Results: 100 patients with 102 lesions were included in this study, of which 88 were invasive carcinomas and 14 were ductal carcinoma in situ. There was a significant difference between mean ADC value and tumour grading ($p < 0.001$), with an inverse correlation (Kendall's tau-b = -0.339; $p < 0.001$). The association was independent of other prognostic factors, as shown by multiple linear regression. The mean ADC value of axillary lymph node-positive breast cancers was significantly lower than that of axillary lymph node-negative cancers ($p = 0.023$), with a significant inverse correlation ($r_{pb} = -0.226$; $p = 0.023$), but the association was not independent of other prognostic factors. ADC value showed good predictive value in predicting tumour aggressiveness, with an area under the receiver operating characteristic curve of 0.717.

Conclusion: Lower ADC values are well correlated with higher histological grade; therefore, ADC can be considered as a promising prognostic parameter for the evaluation of invasive breast cancer.

Key Words: Breast neoplasms; Diffusion magnetic resonance imaging/methods; Prognosis

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中文摘要

彌散加權成像的表觀擴散系數與乳腺癌預後因素的關係

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目的：評估表觀彌散系數（ADC）與乳腺癌預後因素的關係。

方法：回顧分析2012年1月至2016年12月在廣華醫院接受乳腺磁共振成像和後續手術的所有乳腺癌患者，記錄並從以下項目比較惡性病灶的ADC值，包括腫瘤大小（ ≥ 2 cm比 < 2 cm）、改良版 Bloom-Richardson-Elston腫瘤分級（1至3級）、腫瘤侵襲性（乳腺導管原位癌 / 1級浸潤性癌比2至3級浸潤性癌）、腋窩淋巴結狀態（陽性比陰性）、雌激素受體表達（陽性比陰性）、孕激素受體表達（陽性比陰性）和人類表皮生長因子受體2受體狀態（陽性比陰性）。

結果：納入100例共102個病灶，其中88例為浸潤性癌，14例為乳腺導管原位癌。平均ADC值和腫瘤分級間存在顯著差異（ $p < 0.001$ ）並呈負相關（Kendall's tau-b = -0.339； $p < 0.001$ ）。多元線性回歸顯示該關聯性獨立於其他預後因素。腋窩淋巴結陽性乳腺癌的平均ADC值顯著低於腋窩淋巴結陰性乳腺癌（ $p = 0.023$ ）並具顯著負相關（ $r_{pb} = -0.226$ ； $p = 0.023$ ），但該關聯性並非獨立於其他預後因素。ADC值在預測腫瘤侵襲性方面顯示良好的預測值，受試者工作特徵曲線下面積為0.717。

結論：較低ADC值與較高組織學分級密切相關。因此，ADC可被視為評估浸潤性乳腺癌的可靠預後參數。

INTRODUCTION

Breast cancer is the most common cancer in women worldwide. It is a complex heterogenous disease with highly variable biological behaviour, clinical course, and prognosis.^{1,2} The classical prognostic factors of breast cancer include tumour size, histological subtypes, histological grading, axillary lymph node involvement, oestrogen receptor (ER) expression, progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) status. These factors demonstrate significant correlation with recurrence of the tumour and patient overall survival rate.^{3,4}

Dynamic contrast-enhanced magnetic resonance imaging (MRI) is a well-established technique for the detection, diagnosis, and staging of breast cancer.⁵⁻⁷ In addition, diffusion weighted imaging (DWI) has been increasingly used to provide more in-depth information for the characterisation of breast lesions.⁸ Apparent diffusion coefficient (ADC) value is a quantifiable value that measures the rate of diffusion of water molecules in a tissue.⁹⁻¹² Low ADC values indicate that diffusion is restricted. Several studies have shown that DWI and ADC are able to differentiate between benign and malignant breast lesions.¹³⁻¹⁷

The purpose of the present study is to evaluate the

association between ADC values and prognostic factors of breast cancer.

METHODS

Patients

We retrospectively reviewed all patients diagnosed with breast cancer who underwent breast MRI and subsequent surgery in Kwong Wah Hospital during the period from January 2012 to December 2016. The study was approved by the Cluster Research Ethics Committee/ Institutional Review Board. All patients underwent the same MRI protocol including a DWI sequence. We excluded patients with suboptimal MRI study and MRI obtained during or after chemotherapy (to avoid any change in tumour tissue resulted from prior treatment). Patients with mucinous carcinoma were also excluded as this type of tumour contains mucin content which has low cellularity and high extracellular water content, resulting in high T2 signal and high ADC value.

MRI Image Acquisition

All MRI images were acquired with the patient in a prone position using a 1.5-T scanner (Achieva XR; Philips Medical Systems, Best, The Netherlands) equipped with a dedicated breast coil. The DWI images were acquired in the axial plane, and a spin-echo single-shot echo-planar imaging sequence with the following

parameters: TR/TE 9795/78 ms, matrix 96×174 pixels, field of view 350×190 mm², slice thickness 3 mm, and slice gap 0.3 mm. Diffusion-sensitising gradient was applied along three orthogonal directions, with b-values of 0 and 1000 s/mm². We also obtained axial T1- and T2-weighted sequences with turbo spin echo and T2-weighted sequences with spectral attenuated inversion recovery turbo spin echo. T1-weighted images were obtained before and after contrast medium injection at 1, 2, 3, 4, and 5 minutes.

MRI Analysis

We generated ADC maps according to the equation: $ADC = \ln(S2/S1) / [1/(b2-b1)]$, where S1 and S2 are the signal intensities in the regions of interest obtained by two gradient factors, b1 (0 s/mm²) and b2 (1000 s/mm²).

The dynamic and diffusion images were evaluated using a dedicated workstation by two radiologists, who were blinded to the pathological findings. Restricted diffusion was defined by hyperintensity on DWI and hypointensity on ADC map, and the dynamic contrast-enhanced images were used as reference purposes. The region of interest was drawn manually by the two readers in consensus, and attention was paid to ensure that predominantly necrotic or cystic appearing regions were not included in the ADC value measurement. ADC values were calculated automatically when the regions of interest were drawn. Examples are shown in Figures 1 and 2.

According to the latest edition of American Joint Committee on Cancer tumour-node-metastasis staging system,¹⁸ a cut-off of 2 cm separates patients with stage



Figure 1. A 60-year-old woman with invasive ductal carcinoma in her left breast. The tumour was of histological grade 3 with axillary lymph node metastasis. Immunohistochemical staining showed positivity for oestrogen receptor expression and progesterone receptor expression, and negativity for human epidermal growth factor receptor 2. (a) Dynamic contrast enhancement image showing an irregular heterogeneously enhancing lesion in the left breast. (b) Diffusion weighted imaging showing a high signal intensity lesion. (c) Apparent diffusion coefficient map showing restricted diffusion ($0.613 \times 10^{-3} \text{ mm}^2/\text{s}$) within the index lesion.

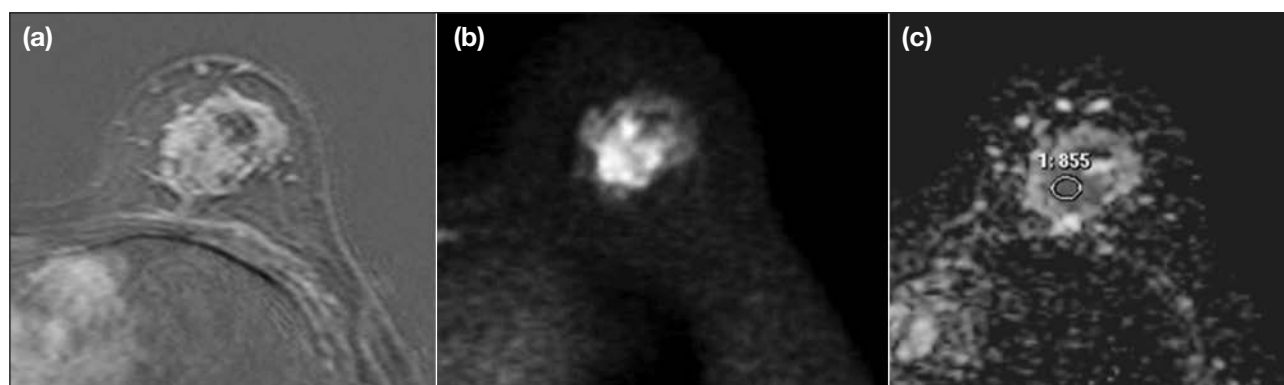


Figure 2. A 43-year-old woman with invasive ductal carcinoma in her left breast. The tumour was of histological grade 2 without axillary lymph node metastasis. Immunohistochemical staining showed negativity for oestrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expressions. (a) Dynamic contrast-enhanced magnetic resonance imaging showing an irregular, heterogeneously enhancing lesion with lobulated margin. (b) Diffusion weighted imaging showing a high signal intensity lesion in the left breast. (c) Apparent diffusion coefficient map showing restricted diffusion ($0.855 \times 10^{-3} \text{ mm}^2/\text{s}$) within the index lesion.

1 disease (localised stage), who have better prognosis, from those with stage 2 disease or above, who have significantly lower survival rates. Therefore, tumour sizes were measured by dynamic contrast-enhanced MRI and divided into two groups: <2 cm and ≥2 cm.

Histological Analysis

Pathological reports were reviewed to determine the tumour size, histological grade, and axillary lymph node metastasis. Grading was assessed by the modified Bloom-Richardson-Elston grading system³ which evaluated tubule formation, nuclear pleomorphism, and mitotic count. Each of these features was scored from 1 to 3, and then each score was added to give a final total score ranging from 3 to 9, to determine the tumour grade. Grade 1 tumours had a score of 3 to 5, grade 2 tumours had a score of 6 to 7, and grade 3 tumours had a score of 8 to 9. To further evaluate the ability of ADC in determining aggressiveness of breast cancer, we considered two groups of disease: the ‘less aggressive’ group, which included ductal carcinoma in situ and grade 1 invasive carcinoma, while the ‘more aggressive’ group included grades 2 and 3 invasive carcinomas.

In addition, immunohistochemical analysis was performed for ER expression, PR expression, and HER2 status. Equivocal cases of HER2 status at immunohistochemistry were subjected to fluorescence in situ hybridisation (FISH) analysis.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation; categorical variables are presented as number (%). Test for normality was performed by Q-Q plot and a normal distribution was observed in the data. Mean ADC values were compared between groups using Student’s *t* test (for two groups) or analysis of variance

(ANOVA; for multiple groups). Post-hoc Tukey test was used to compare groups when significant difference was observed in ANOVA. For prognostic factors which show significant difference with ADC values, correlation tests were conducted to determine the degree of relationship. Kendall’s rank correlation and point-biserial correlation were used for ordinal and dichotomous variables, respectively. Independent association of prognostic factors and ADC value was further determined by a multiple linear regression model. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of ADC value in determining the aggressiveness of breast cancer. A two-sided *p* < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Windows version 22; IBM Corp., Armonk [NY], United States).

RESULTS

A total of 124 patients (126 lesions) diagnosed with breast cancer during the period from January 2012 to December 2016 were initially included in the present study. Of them, 24 patients were subsequently excluded from the analysis: 10 had undergone neoadjuvant chemotherapy, four had mucinous carcinoma, three had motion artefacts on MRI, two had cancers not visible on MRI, and the pathology reports of five patients had no available information on tumour grading. The final study population therefore included 100 patients (mean age ± standard deviation, 50 ± 11 years) with a total of 102 lesions, as two patients had breast cancer in both breasts.

Histopathology revealed 88 invasive carcinomas and 14 ductal carcinomas in situ. There were 19 (21.5%) grade 1, 32 (36.4%) grade 2, and 37 (42.1%) grade 3 lesions for the invasive carcinomas. The different histological subtypes of breast cancer and their mean ADC values are shown in Table 1. There was axillary lymph node involvement

Table 1. Histological diagnosis and apparent diffusion coefficient values.

Subtype of carcinoma	No. (%) of cases	Apparent diffusion coefficient (mean ± standard deviation), 10 ⁻³ mm ² /s*
Metaplastic carcinoma	4 (3.9%)	0.83 ± 0.207
Invasive carcinoma of no special type	75 (73.5%)	0.83 ± 0.154
Invasive papillary carcinoma	1 (1.0%)	1.2
Invasive lobular carcinoma	4 (3.9%)	1.00 ± 0.196
Ductal carcinoma in situ	14 (13.7%)	1.04 ± 0.124
Mammary carcinoma	1 (1.0%)	0.73
Invasive carcinoma with medullary feature	1 (1.0%)	0.83
Tubular carcinoma	2 (2.0%)	0.66 ± 0.053
Total	102 (100%)	0.87 ± 0.172

* Standard deviation was not calculated for categories with 1 case.

in 34/102 (33.3%) tumours. In the present study, 66.7% of tumours were ER-positive and 62.7% were PR-positive. A total of 16 tumours (15.7%) were found to be HER2-positive either by immunohistochemistry or by FISH analysis. The mean ADC value of all malignant lesions was $0.87 \times 10^{-3} \text{ mm}^2/\text{s}$ (range, $0.512 \times 10^{-3} \text{ mm}^2/\text{s}$ to $1.28 \times 10^{-3} \text{ mm}^2/\text{s}$). The mean histological tumour size was 2.5 cm. Among these, 46 lesions were <2 cm in size, while 56 lesions were ≥ 2 cm in size.

The mean ADC values for ductal carcinoma in situ lesions, grade 1, 2 and 3 tumours were $1.04 \times 10^{-3} \text{ mm}^2/\text{s}$, $0.90 \times 10^{-3} \text{ mm}^2/\text{s}$, $0.85 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.80 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively (Figure 3). Tukey test showed that the mean ADC value in ductal carcinoma in situ lesions was significantly higher than those in grades 1 ($p = 0.042$), 2 ($p = 0.001$), and 3 ($p < 0.001$), respectively. There was a statistically significant inverse correlation (Kendall's tau-b coefficient = -0.339 ; $p < 0.001$) between the ADC value and tumour grading. Multiple linear regression, which included all the prognostic factors being studied, further showed that tumour grading was independently associated with ADC value ($p < 0.001$). The mean ADC value of the 'more aggressive' group ($0.82 \times 10^{-3} \text{ mm}^2/\text{s}$)

was statistically lower than that of the 'less aggressive' group ($0.96 \times 10^{-3} \text{ mm}^2/\text{s}$), with $p < 0.001$ (Figure 4).

The mean ADC value of axillary lymph node-positive breast cancers was $0.81 \times 10^{-3} \text{ mm}^2/\text{s}$, and that of axillary lymph node-negative breast cancers was $0.89 \times 10^{-3} \text{ mm}^2/\text{s}$. The mean ADC of the axillary lymph node-positive breast cancers was significantly lower than that of axillary lymph node-negative breast cancers ($p = 0.023$; Figure 5), with a significant inverse association between ADC value and axillary lymph node involvement ($r_{pb} = -0.226$; $p = 0.023$). However, no independent association was observed in multiple linear regression ($p = 0.328$). There were no significant differences between mean ADC values and the groups of tumour size ($p = 0.746$), ER expression ($p = 0.730$), PR expression ($p = 0.682$), and HER2 status ($p = 0.766$) [Table 2].

The ADC value was good at predicting the aggressiveness of a breast lesion, with area under the ROC curve of 0.717 (Figure 6). Different ADC threshold values were tested, and it was found that ADC threshold value of $<0.9 \times 10^{-3} \text{ mm}^2/\text{s}$ showed a 60.6% sensitivity and 78.3% specificity in detecting more aggressive breast lesions.

DISCUSSION

The present study revealed significant inverse correlation between ADC value and tumour grading ($p < 0.001$). There was also a significant difference ($p < 0.001$)

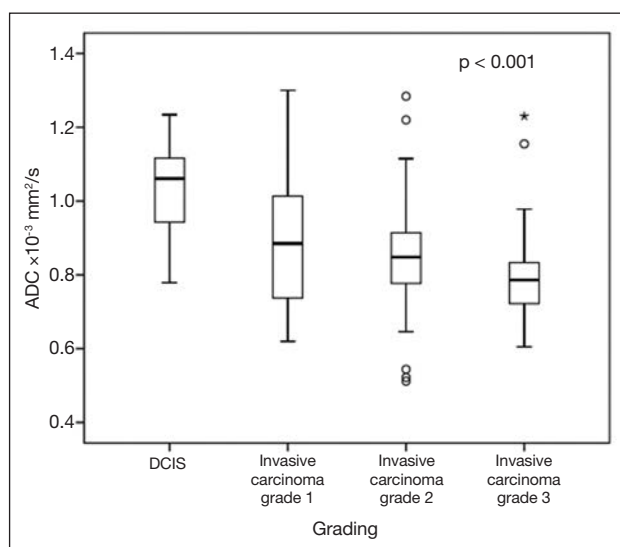


Figure 3. Boxplot showing the distribution of apparent diffusion coefficient (ADC) values of breast cancer according to tumour grading. The mean ADC values for ductal carcinoma in situ lesions, grade 1, grade 2 and grade 3 invasive tumours were $1.04 \times 10^{-3} \text{ mm}^2/\text{s}$, $0.90 \times 10^{-3} \text{ mm}^2/\text{s}$, $0.85 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.80 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively. A statistically significant difference between the ADC value and tumour grading was found ($p < 0.001$). Tukey test showed that ductal carcinoma in situ (DCIS) lesions had a significantly higher ADC value compared with grade 1, grade 2, and grade 3 invasive lesions ($p = 0.042$, $p = 0.001$, and $p < 0.001$, respectively).

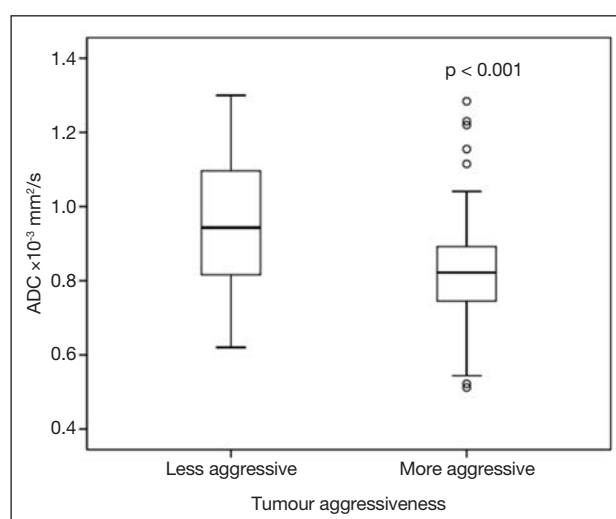


Figure 4. Boxplot showing the distribution of apparent diffusion coefficient (ADC) values of breast cancer according to tumour aggressiveness. The mean ADC value of the 'more aggressive' group ($0.82 \times 10^{-3} \text{ mm}^2/\text{s}$) was significantly lower than that of the 'less aggressive' group ($0.96 \times 10^{-3} \text{ mm}^2/\text{s}$; $p < 0.001$).

between the mean ADC value in the ‘less aggressive’ group (in situ and grade 1 tumours, mean ADC = 0.96×10^{-3} mm²/s) and the mean ADC value in the ‘more aggressive’ group (grade 2 and 3 tumours, mean ADC = 0.82×10^{-3} mm²/s). This indicates that ADC correlates

well with breast cancer aggressiveness. These findings are consistent with those of previous studies.^{19,22} In addition, our ROC curve analysis identified 0.9×10^{-3} mm²/s as the ADC threshold level for adequate detection of more aggressive lesions. Guo et al¹³ and Woodhams et al²³ have reported associations between ADC values and tumour cellularity, and that malignant breast lesions had higher cellularity compared with benign lesions. Tumour cellularity is an important index of tumour grade; more densely packed tumour cells and smaller extracellular volume fraction inhibits the effective motion of water molecules and restrict diffusion, resulting in lower ADC values compared with lower-grade breast cancers.^{19,24,25}

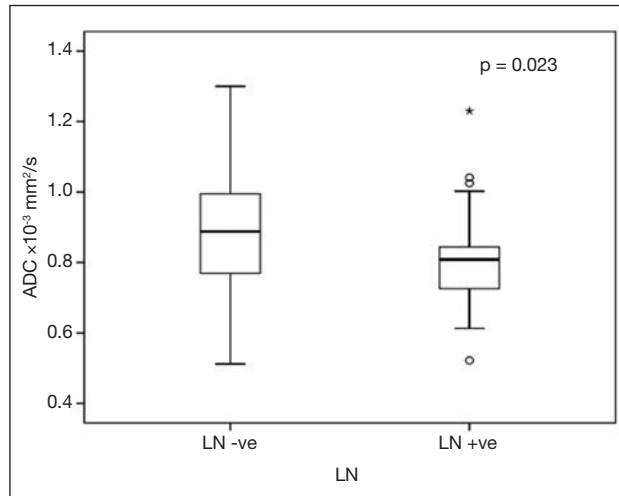


Figure 5. Boxplot showing the distribution of apparent diffusion coefficient (ADC) values of invasive breast cancers according to lymph node status. The mean ADC value of the lymph node (LN)-positive breast cancers (0.81×10^{-3} mm²/s) was significantly lower than that of the LN-negative breast cancer (0.89×10^{-3} mm²/s; $p = 0.023$).

Axillary lymph node metastasis is one of the most important predictors of long-term survival in breast cancer patients. According to Soerjomataram et al,²⁶ patients with lymph nodes metastasis have about 4- to 8-fold higher mortality than those without nodal involvement, and the more lymph nodes involved, the worse the prognosis. Evaluation of the axillary nodal status prior to surgery is still a challenge in the management of breast cancer patients. Various imaging modalities can be adopted when assessing axillary nodal status, including ultrasound, computed tomography, positron emission tomography, and breast MRI. In recent years, axillary lymph node dissection has been replaced by sentinel

Table 2. ADC values according to prognostic factors of breast cancer.

	No.	ADC (mean ± standard deviation)	p Value
Tumour grading			<0.001
Ductal carcinoma in situ	14	1.04 ± 0.12	
Invasive carcinoma grade 1	19	0.90 ± 0.19	
Invasive carcinoma grade 2	32	0.85 ± 0.17	
Invasive carcinoma grade 3	37	0.80 ± 0.13	
Tumour aggressiveness			<0.001
Less aggressive	33	0.96 ± 0.18	
More aggressive	69	0.82 ± 0.15	
Lymph node status			0.023
Negative	68	0.89 ± 0.18	
Positive	34	0.81 ± 0.13	
Oestrogen receptor expression			0.730
Negative	34	0.88 ± 0.19	
Positive	68	0.86 ± 0.16	
Progesterone receptor expression			0.682
Negative	38	0.88 ± 0.19	
Positive	64	0.86 ± 0.16	
HER2 receptor status			0.766
Negative	86	0.87 ± 0.17	
Positive	16	0.86 ± 0.17	
Tumour size			0.746
<2 cm	46	0.86 ± 0.17	
≥2 cm	56	0.87 ± 0.17	

Abbreviations: ADC = apparent diffusion coefficient; HER2 = human epidermal growth factor receptor.

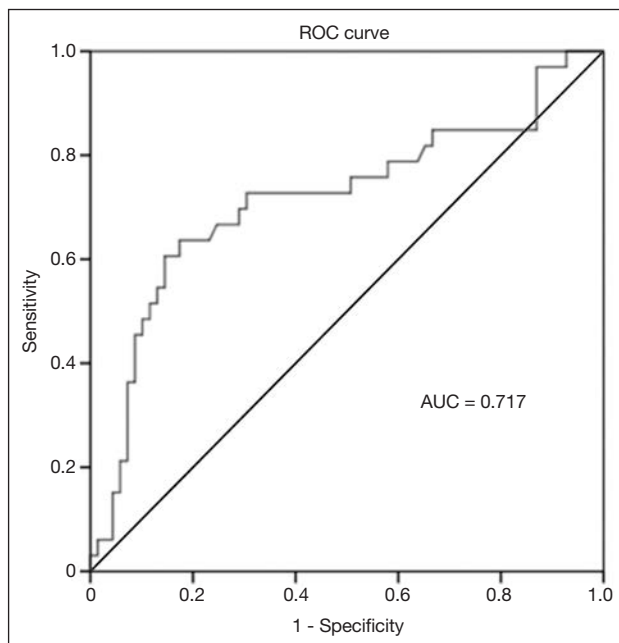


Figure 6. Receiver operating characteristic (ROC) curve: diagnostic performance of apparent diffusion coefficient for the prediction of lesion aggressiveness. Diagonal segments are produced by ties. Abbreviation: AUC = under the ROC curve.

lymph node biopsy for nodal staging in clinically node-negative breast cancer patients, as the latter modality is less invasive.^{27,28}

In the present study, although there was a significant difference between the axillary lymph node-positive cancer group and axillary lymph node-negative cancer group on *t* test, the numerical difference in the ADC values on *t* test was quite small (0.81×10^{-3} mm²/s vs. 0.89×10^{-3} mm²/s). Moreover, there was no independent association between ADC value and axillary lymph node involvement in the regression analysis. This suggests that ADC values may not be able to be used to differentiate benign from metastatic lymph nodes in patients with breast cancer. Our findings are in line with previous studies by Schipper et al²⁹ and Dong et al,³⁰ who found that ADC measurement was limited in the prediction of sentinel lymph node metastasis in breast cancer. Further studies are required to evaluate the diagnostic performance of MR imaging in axillary nodal imaging as a non-invasive alternative for sentinel lymph node biopsy.

Another crucial prognostic factor of breast cancer is tumour size. Larger tumours are associated with poorer prognosis and decreased overall survival rates of breast

cancer patients.^{3,31} Razek et al²¹ reported that the ADC values of larger breast cancers were significantly lower than that of smaller tumours. In contrast, Choi et al³² and Kim et al³³ reported that there was no significant association between ADC value and tumour size. In the present study, we found no significant association between ADC values and tumour size. The discordant results may be due to different study populations in each of the studies. The present study included patients with invasive cancers of various histologies, similar to the study by Kim et al,³³ whereas Razek et al²¹ included patients only with invasive ductal carcinomas.

The present study showed no significant associations between ADC values and ER expression, PR expression, and HER2 status. These prognostic indicators have been used as guide to hormonal and targeted therapy.³⁴ Ludovini et al³⁵ found that ER expression inhibits the angiogenic pathway and induces a decrease in perfusion, therefore affecting the ADC value. Kumar and Yarmand-Bagheri³⁶ reported that overexpression of HER2 in human tumour cells is closely associated with increased angiogenesis and expression of vascular endothelial growth factor. Several studies have reported contrary results on the association between ADC values and immunohistochemical markers. Jeh et al³⁷ used both 1.5-T MRI with b-values of 0 and 1000 s/mm² and 3-T MRI with b-values of 0 and 750 s/mm², and found that low ADC value was related to positive expression of ER and negative expression of HER2. Park et al³⁸ used 3-T MRI with b-values of 0 and 1000 s/mm² and reported that high ADC value was associated with positive expression of HER2-positive invasive ductal carcinoma, but not associated with ER expression or PR expression. Choi et al³² used 1.5-T MRI with b-values of 0 and 1000 s/mm² and found that low ADC value was associated with positive expression of ER and PR, but there was no significant association of ADC with HER expression. Martincich et al²⁰ used 1.5-T MRI with b-values of 0 and 900 s/mm² and found that higher ADC value was associated with ER-negative and HER2-positive breast cancers. The diverging results might be attributed to the different magnetic fields with variable b-values, which could have affected the ADC values recorded in different studies.

There are several limitations to the present study. First, this is a retrospective study with relatively inhomogeneous sample size, particularly regarding tumour grading, with a small number of ductal in situ carcinoma and grade 1 invasive carcinoma. Second, the region of

interest placement in terms of size and shape was not standardised in this study, and that could have influenced the ADC value measurement. Further studies on whether different region of interest placement methods influence ADC values are required. Third, the b-value was chosen as 1000 s/mm² for the present study. The influence of the b-value on the results and the optimal b-value combination should be evaluated in future studies. Finally, the results obtained might not be applicable to different scan parameters or magnet strength, and this should also be assessed in future studies. Furthermore, studies on disease recurrence or survival rate by long-term follow-up would help to clarify the relationship between ADC values and the prognosis of patients with breast cancer.

In conclusion, the present study showed that DWI is useful in assessing the aggressiveness of breast cancer, as lower ADC value is well correlated with higher histological grade. ADC can be considered as a promising prognostic parameter for the evaluation of invasive breast cancer.

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