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# Value of apparent diffusion coefficient factor in correlation with the molecular subtypes, tumor grade, and expression of Ki-67 in breast cancer

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## Abstract

**Background:** Breast cancer is known to be the most common cancer in women; in the last decade, contrast-enhanced magnetic resonance imaging has become an important tool in the diagnosis of cancer breast. Numerous studies have analyzed associations between imaging and histopathological features as well as the proliferation potential of breast cancer. The purpose of this study was to evaluate the relationship between the apparent diffusion coefficient (ADC) and expression of Ki-67 as well as tumor molecular subtype in breast cancer.

**Results:** No significant difference between the mean ADC value of tumors of grade I, II, and III was found. However, there was a significant difference between the mean ADC value of tumors of molecular type A and molecular type B ($P=0.000$), HER2 overexpression ($P=0.018$), and TN ($P=0.000$), respectively. However, there was no significant difference between molecular type B, HER2 overexpression and TN. Also, no significant difference was found between the Ki-67 value of tumors of grade I, II, and III. Yet there was a significant difference between the mean ADC value of tumors of molecular type A and molecular type B ($P=0.000$), HER2 overexpression ($P=0.014$), and TN ($P=0.000$), respectively. However, there was no significant difference between molecular type B, HER2 overexpression, and TN.

**Conclusions:** There is a significant inverse correlation between ADC values and Ki-67 expression. DWI and Ki-67 could be a good discriminator between tumors of molecular subtype A from other subtypes, yet it did not show a correlation with the tumor grade.

**Keywords:** Magnetic resonance imaging, Diffusion, ADC value, Ki-67, Breast cancer molecular subtypes

## Background

A common malignancy among women is breast cancer (BC). Using DNA microarray techniques, the gene pattern of expression in breast cancer has been classified into different molecular types with clinical, biologic, and treatment effects based on estrogen (ER), progesterone (PR) and HER-2 receptor analysis. Breast cancer has four primary molecular subtypes, defined mainly by hormone receptors (HR) and other types of proteins involved (or not) in each cancer: Luminal A or HR+/HER2- (HR-positive/HER2-negative); Luminal B or HR+/HER2+(HR-positive/HER2-positive); triple negative or HR-/HER2- (HR/HER2-negative); and HER2-positive [1].

Ki-67 is a nuclear protein related to cellular proliferation and was first identified by Gerdes et al. in the early 1980s [2]. Ki-67 is found in all proliferating cells and is used as a proliferation marker; it is also considered a prognostic factor for breast cancer [3, 4]. Compared

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with other markers, Ki- 67 immuno-staining is a suitable method for testing proliferating index [5, 6].

Various imaging modalities including mammography, ultrasound, and magnetic resonance (MRI) play a vital role in diagnosing and staging breast cancer. Imaging cannot only detect breast tumors but can also predict their histopathological characteristics, yet none of these imaging modalities can provide accurate information about tissue cellularity, which is considered the main indicator of tumor grade. Therefore, many investigators try to assess by using diffusion-weighted breast imaging and without intravenous contrast material injection, diffusion-weighted breast imaging can facilitate the diagnosis of breast lesions, yet may require some increase in examination time [7, 8, and 9].

Diffusion-weighted imaging of the breast is an MRI sequence that gives several advantages compared to dynamic contrast-enhanced sequence as it does not require intravenous contrast, short duration, and easy to perform. Moreover, integrating quantitative imaging biomarkers gives us the ability to measure the underlying pathological mechanisms in vivo noninvasively, identifying properties that are important for detection, diagnosis, prognosis, or response to therapy [10].

In this study, we aimed to assess the status of apparent diffusion coefficient (ADC) in breast cancer patients and to evaluate its association with other factors including Ki- 67, molecular subtype, and grade of breast tumor to validate its significance as a prognostic factor of breast cancer.

## Methods

This was a retrospective study. It was approved by the institutional review board. Between April 2016 and February 2020, the total number of included patients was 55.

Inclusion criteria: (1) patients with breast malignancy proved by pathology either by surgery or by biopsy; (2) patients who had a standard MRI breast study, including axial T1WI, fat-suppressed T2 WI, axial fat-saturated T1WI pre- and post-enhancement, and DWI sequences; and (3) patients with complete clinical data; immunohistochemistry and Ki-67 values in their histopathology reports. Exclusion criteria: (1) operated/ treated breast before MRI; (2) poor image quality; and (3) incomplete immunohistochemistry or Ki-67 values in their reports.

### MRI technique

DCE-MRI breasts were performed on a 1.5-T system (MAGNETOM Aera; Siemens, Erlangen, Germany). Women lying prone with their breasts fixed in a dedicated four-channel phased-array breast coil. All written consents were obtained before the study was performed. Patients were advised not to move to avoid motion artifacts.

The following MRI sequences were taken: slice thickness 4 mm, FOV 350 mm, and matrix $512 \times 512$: Axial Turbo Inversion Recovery Magnitude (TIRM) with TR 7700 ms and TE 74 ms; Axial T2 fast spin-echo (FSE) with TR 6160 ms and TE 76 ms; and Axial T1 fast spin-echo (FSE) with TR 415 ms and TE 4.6 ms. Diffusion-weighted imaging (DWI) was done at TR 8200 ms and TR 85 ms in the axial plane bilaterally with b values of 0, 500, and 1000 s/mm$^2$. ADC map was systematically performed. ADC value was measured in mm$^2$/s using a rounded ROI with a diameter of 5–10 mm$^2$ placed on the darkest point of the mass which shows diffusion restriction on the DW sequences. Areas of T2 shine-through, such as cystic or necrotic portions of the tumor shown as high signal intensity on T2-weighted images and ADC maps, were avoided. When comparing with DCE MR images, the enhancing solid portion of the mass was used to locate ADC measurements. The ADC value was automatically calculated when the ROI was drawn. Two radiologists with 20 and 25 years of experience in MRI breast analyzed the images. The diagnosis was reached by consensus.

### Histological analysis

According to the numerical scoring pattern to define tubule formation, pleomorphism, and mitotic count, Nottingham combined grading was used to assess histological grades of invasive ductal carcinoma, NOS (non-otherwise specified). The score ranges from 3 to 9, with a total score of 3–5 representing low grade (grade 1), a score of 6 or 7 representing grade 2, and a score of 8 or 9 representing grade 3 (Table 1): Nottingham combined histological grade [11] (Figs. 1, 2, 3, 4).

**Table 1** Nottingham combined histological grade, Ref [11]

| Feature graded | Criterion | Score |
|---|---|---|
| Tubule(graded) formation | > 75% | 1 |
| | 10–75% | 2 |
| | < 10% | 3 |
| Nuclear pleomorphism | Small, regular uniform cells | 1 |
| | Moderate increase and variablity | 2 |
| | Marked variation | 3 |
| Mitotic count (/10 hpf) | 0–5 | 1 |
| | 6–10 | 2 |
| | > 11 | 3 |

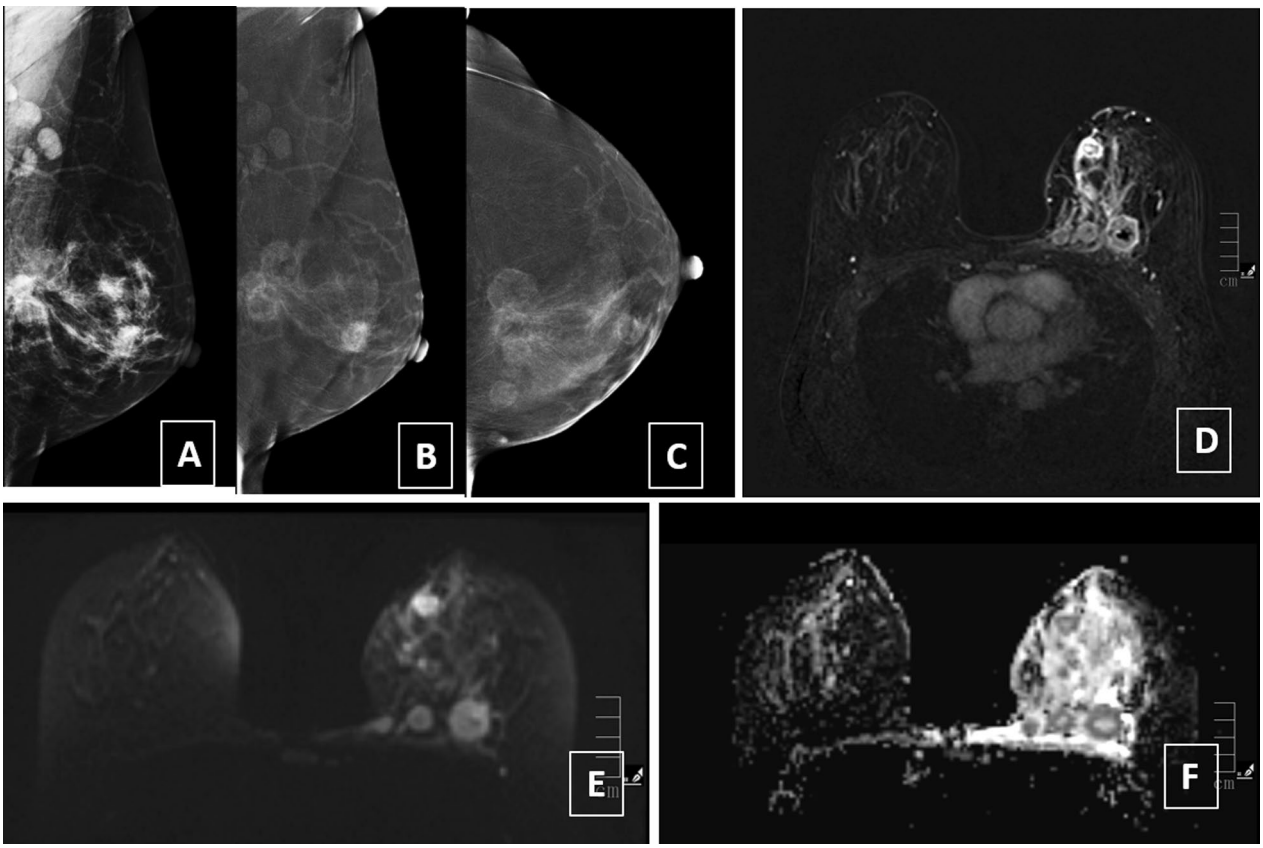


**Fig. 1** A 42-year-old female with multifocal left breast ca **A** MLO low-energy CESM (**B**), (**C**) recombined CESM MLO and CC showing multiple enhancing masses lower inner quadrant **D** DCE-MRI shows marginal enhancement with central necrosis **E** and **F** DWI b value = 800 and ADC, respectively, showing peripheral diffusion restriction. ADC value = $0.989 \times 10^{-3} mm^2/s$. HER-2 positive BC. IDC GRADE III

### Statistical analysis

Data were coded and entered data using SPSS (Statistical Package for the Social Sciences) version 23. Data were summarized using the mean and standard deviation. For quantitative data, we used median, minimum, and maximum; for qualitative data, frequency (number) and relative frequency (%) were used for categories. A comparison of quantitative variables was made using nonparametric Kruskal–Wallis and Mann–Whitney tests [12]. ROC curve was plotted with an area under the curve analyzed to detect the specific cutoff value of ADC for the detection of high-grade tumors. *P* values below 0.05 (< 5%) were considered statistically significant.

## Results

Fifty-five female patients were included in this study, with an age range from 21 to 83 years (mean age 50.8 ± 14). The included carcinomas included 48 (87.3%) invasive ductal carcinomas; 26 (54%) of them were NST (no specific type), 3 (5.5%) mucinous carcinoma, 2 (3.6%) invasive lobular carcinoma, 1 (1.8%) NEC (neuroendocrine carcinoid), and 1 (1.8%) carcinosarcoma/metaplastic carcinoma.

Their grading was as follows: 11 lesions (20%) grade I, 38 lesions (69.1%) grade II, and 6 (10.9%) lesions grade III. Ten (18.2) lesions were molecular type A, 35 (63.6) lesions were molecular type B, 5 (9.1) were HER2 overexpression, and 5 (9.1) were triple negative (Table 2).

Analysis of diffusion-weighted images and comparison of the mean ADC value as well as Ki-67 with the pathological grade and molecular subtype of the tumor were performed. In all the studied lesions, 55 (100%) showed a bright signal in DWI and low/intermediate signal in ADC map denoting diffusion restriction. ADC values ranged from 0.5 to $1.6 \times 10^{-3}$ $mm^2/s$ (mean $1 \pm 0.2 \times 10\text{-}3mm2/s$). The mean ADC value of grade I was $1.0 \pm 0.2 \times 10^{-3}$ $mm^2/s$, grade II was $0.9 \pm 0.1 \times 10^{-3}$ $mm^2/s$, and grade III was $0.9 \pm 0.2 \times 10^{-3}$ $mm^2/s$ (Table 3). There was no significant difference regarding the mean ADC values of tumors grade I, II, and III. The mean ADC value of molecular type A, molecular type B, HER2 overexpression, and triple-negative subtypes

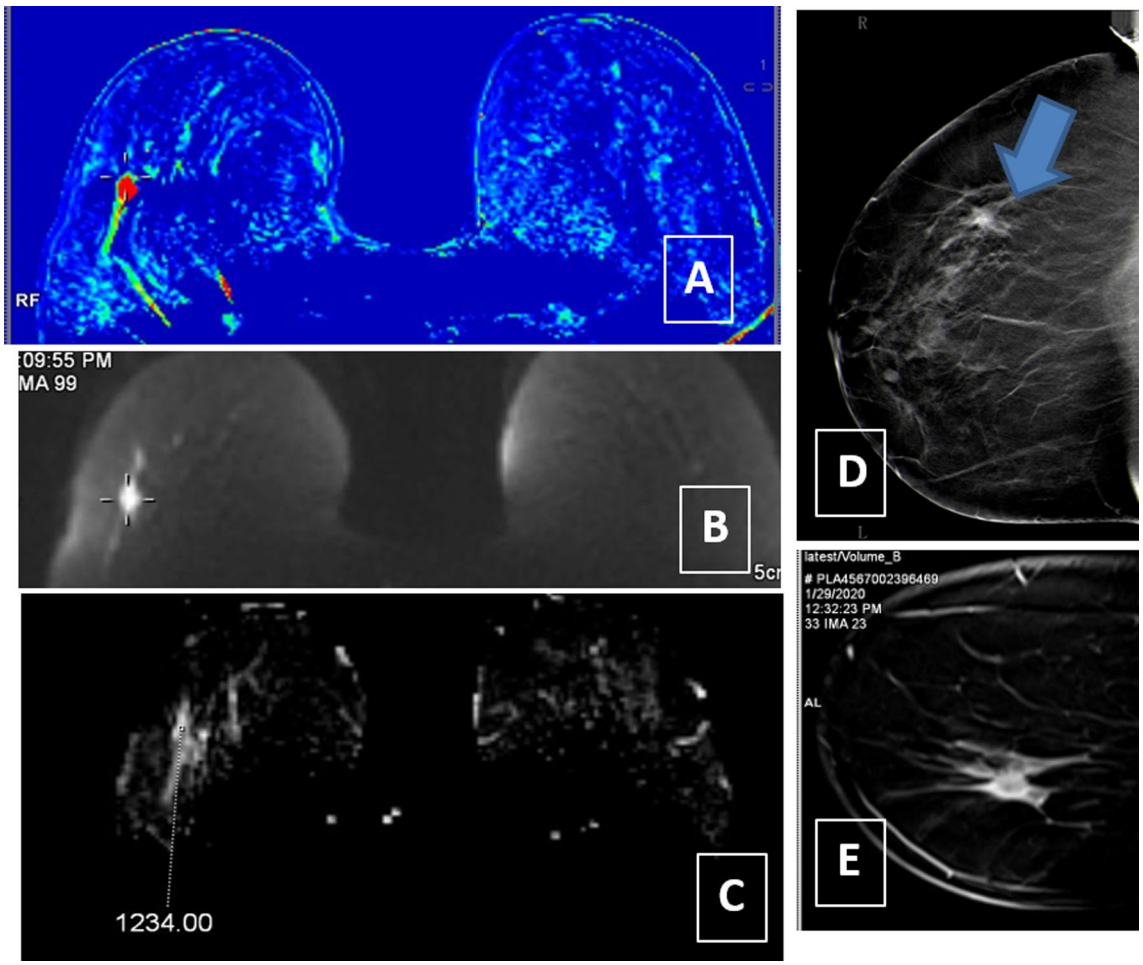


**Fig. 2** A 52-year-old female with recently diagnosed left breast LOQ IDC Grade II (Luminal type A) **A** MRI Wash-in map **B**, **C** DWI b value = 800 and ADC, respectively, showing diffusion restriction ADC value = $0.123 \times 10^{-3}$mm$^2$/s **D** 3D Tomo slice CC view a single spiculate mass (arrow) **E** DCE-MRI sagittal shows intense marginal enhancement

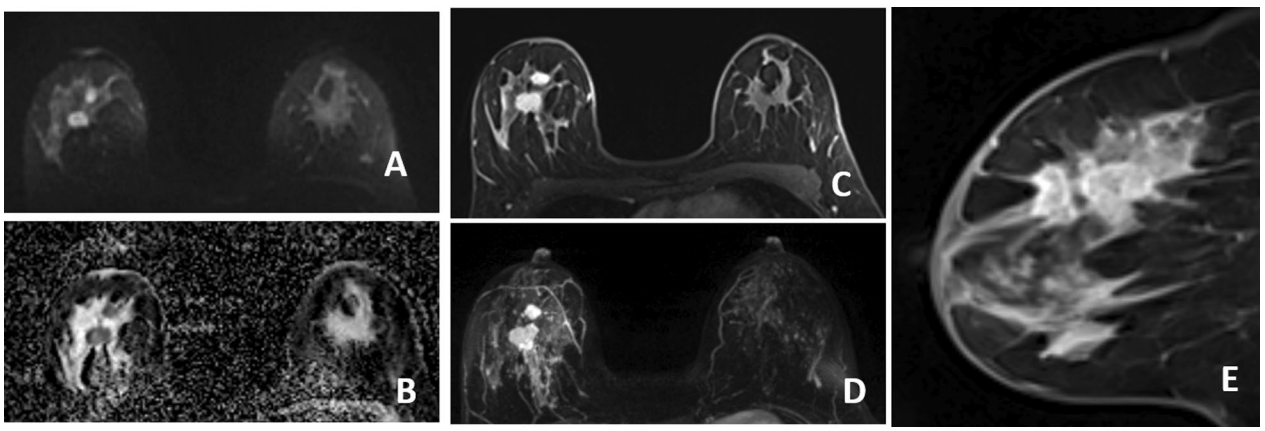


**Fig. 3** A 49-year-old female with bifocal right breast IDC Grade II (luminal subtype B) **A** DWI b value:800 **B** ADC showing diffusion restriction **ADC value = $0.994 \times 10^{-3}$mm$^2$/s. C** DCE-MRI showing intense enhancement. **D** 3D MIP **E** delayed sagittal MRI showing central wash-out with marginal enhancement. Ki-67 high 25%

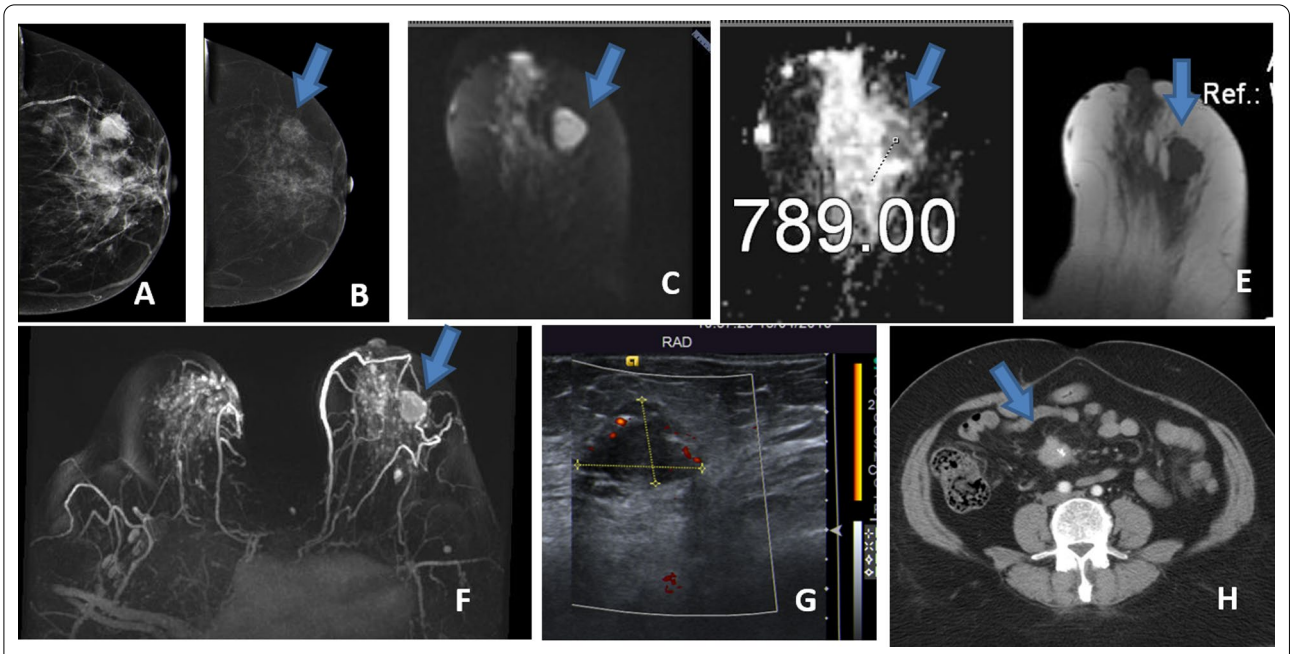


**Fig. 4** A 72-year-old female with an incidentally discovered single circumscribed left breast mass with homogenous enhancement as seen on mammogram CC view (**A**) and recombined CESM (**B**). **C** and **D** DWI b value = 800 and ADC, respectively, showing diffusion restriction. ADC value = $0.789 \times 10^{-3}$mm$^2$/s **E** Axial MRI Left breast shows hypointense mass with smooth margin **F** DCE-MRI 3D MIP shows the left breast mass with feeding vessels (arrow) **G** US shows the mass with circumscribed margin, posterior enhancement and advancing anterior edge. Note peripheral vascularity by color Doppler. Core biopsy revealed metastatic NEC, triple negative. **H** Axial CT scan shows the primary mesenteric carcinoid tumor with calcifications

was $1.2 \pm 0.2 \times 10^{-3}$ mm$^2$/s, $0.9 \pm 0.1 \times 10^{-3}$ mm$^2$/s, $0.9 \pm 0.1 \times 10^{-3}$ mm$^2$/s, and $0.8 \pm 0.1 \times 10^{-3}$ mm$^2$/s, respectively. Yet a significant difference between the mean ADC value of tumors of different molecular subtypes ($P = 0.000$) was found. A significant difference between the mean ADC value of tumors of molecular type A as opposed to molecular type B ($P = 0.000$), HER2 overexpression ($P = 0.018$), and TN ($P = 0.000$), respectively, was found. However, there was no significant difference between molecular type B, HER2 overexpression, and TN (Tables 4, 5, 6).

Ki-67 values ranged from 6 to 92.5 with a mean of $42.9 \pm 17.3$; the mean Ki-67 of grade I, grade II, and grade III was $41.3 \pm 18.2$, $40.9 \pm 16.2$, and $58.8 \pm 17.2$, respectively. There was no significant difference between the Ki-67 value of tumors of grade I, II, and III (Table7).

The Ki-67 value of tumors of different molecular subtypes showed a significant difference ($P = 0.000$) (Table 8). A significant difference was found between the mean ADC value of tumors of molecular type A as opposed to molecular type B ($P = 0.000$), HER2 overexpression ($P = 0.014$), and TN ($P = 0.000$), respectively. However, there was no significant difference between the last three types together: molecular type B, HER2 overexpression, and TN (Tables 5 and 6).

Correlation between ADC and Ki-67 value showed an R value of -0.779 and R2 value of 0.599 ($P = 0.000$) (significant/good negative correlation) (Tables 9 and 10).

## Discussion

Different molecular types of breast carcinoma show different biological characteristics, clinical outcomes, and prognoses [13]. An accurate assessment of the disease course and prognosis preoperatively is essential for accurate diagnosis planning for treating breast cancer [14].

The value of breast MRI in the preoperative assessment of patients is important owing to its value as a means of describing pattern, size, and number of breast lesions. The early proliferation of tumor accompanies changes in both anabolism and catabolism affecting its size and altering the intra- and extracellular environment. Functional MR as diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) assist the radiologist in finding certain changes related to tumor proliferation [15].

In the current study, the calculated mean ADC value of breast malignant masses measured $1 \pm 0.2 \times 10^{-3}$ mm$^2$/s. This was similar to mean ADC values reported by previous studies, such as Belli et al. [13]

**Table 2** Description of study variables

| | **Description (*n* = 55)** |
|---|---|
| *Age* | |
| Range | 21–83 |
| Mean ± SD | 50.8 ± 14 |
| *ADC* | |
| Range | 0.5–1.6 |
| Mean ± SD | 1 ± 0.2 |
| *Grade* | |
| Grade I | 11 (20) |
| Grade II | 38 (69.1) |
| Grade III | 6 (10.9) |
| *ER* | |
| +VE | 43 (78.2) |
| −VE | 12 (21.8) |
| *PR* | |
| +VE | 36 (65.5) |
| −VE | 19 (34.5) |
| *HER2* | |
| +VE | 22 (40) |
| −VE | 33 (60) |
| *Molecular type* | |
| A | 10 (18.2) |
| B | 35 (63.6) |
| HER2 | 5 (9.1) |
| TN | 5 (9.1) |
| *IDC* | 48 (87.3) |
| *NST* | 26 (47.3) |
| *NEC* | 1 (1.8) |
| *ILC* | 2 (3.6) |
| *MUCINUS* | 3 (5.5) |
| *CARCINOSARCOMA/METAPLASTIC CA* | 1 (1.8) |
| *Ki67* | |
| Range | 6–92.5 |
| Mean ± SD | 42.9 ± 17.3 |

and Costantini et al. [16], where mean ADC values measured $1.02 \times 10^{-3}$ $mm^2/s$ and $1.03 \times 10^{-3}$ $mm^2/s$, respectively. However; other studies reported lower ADC including Kato et al. [17] who reported the mean ADC value of $0.894 \pm 0.20 \times 10^{-3}$ $mm^2/s$; it was $0.85 \pm 0.12 \times 10^{-3}$ $mm^2/s$ in Gouhar et al. [18] study, $0.91 \pm 0.20 \times 10^{-3}$ $mm^2/s$ in Park et al. [19] study, $0.93 \pm 0.27 \times 10^{-3}$ $mm^2/s$ in Ulghaffara et al. [20] study, and $0.91 \pm 0.151 \times 10^{-3}$ $mm^2/s$ in Matsubayashi et al. [21] study.

ADC values ranged from 0.5 to $1.6 \times 10^{-3}$ $mm^2/s$ in our study, thus lying above the cutoff value differentiating benign from malignant lesions suggested by previous studies, such as Sharma et al. [15] with a cutoff ADC value of $1.23 \times 10^{-3}$ $mm^2/s$, and Tan et al. [22] where the cutoff ADC value for benign lesions was $1.21 \times 10^{-3}$ $mm^2/s$ for b = 500 $s/mm^2$ and for malignant lesions was $1.22 \times 10^{-3}$ $mm^2/s$ for b value:1000 $s/mm^2$. Studying the correlation between the mean ADC value and histological grades of breast carcinoma, we found that there was no significant relation between them.

This coincided with the previous research done by Park et al. [19] and Tan et al. [22] who found no significant correlation between the measured ADC values and tumor grades.

On the contrary, Belli et al. [13], Abdel Razek et al. [23], Costantini et al. [16], Gouhar et al. [18], and Guo Yan et Al. [24] found that there was a significant yet inverse relation between them.

In the current study, the mean ADC value for grade I masses was $1.0 \pm 0.2 \times 10^{-3}$ $mm^2/s$, that of grade II was $0.9 \pm 0.1 \times 10^{-3}$ $mm^2/s$, and that of grade III was $0.9 \pm 0.2 \times 10^{-3}$ $mm^2/s$. Kindly view Figs. 1, 2, 3 and 4 (case presentations).

This is equal to the results of Costantini et al. [16] reporting mean ADC values for grade I, II, and III tumors to be: $1.25 \times 10^{-3}$ $mm^2/s$, $1.02 \times 10^{-3}$ $mm^2/s$, and $0.92 \times 10^{-3}$ $mm^2/s$, respectively. However, it differs from the results obtained by Gouhar et al. [18] who reported that the mean ADC values of grades I, II, and III were $0.96 \pm 0.12 \times 10^{-3}$ $mm^2/s$, $0.87 \pm 0.07 \times 10–3$ $mm^2/s$, and $0.75 \pm 0.12 \times 10–3$ $mm^2/s$, respectively. This difference may be attributed to the discrepancy in patient number and diffusion technique using different b values.

High ADC values can be useful in diagnosing TNBC [25]. In our study, we had 5 cases of TNBC with a mean

**Table 3** Comparison of ADC regarding grade

| | **ADC** | | | | | | | ***P* value** |
|---|---|---|---|---|---|---|---|---|
| | **Min** | **Max** | **Mean** | **SD** | **Median** | **Per 25** | **Per 75** | |
| *Grade* | | | | | | | | |
| Grade I | 0.8 | 1.6 | 1.0 | 0.2 | 1.0 | 0.9 | 1.2 | 0.408 |
| Grade II | 0.6 | 1.4 | 0.9 | 0.1 | 0.9 | 0.9 | 1.0 | |
| Grade III | 0.5 | 1.0 | 0.9 | 0.2 | 1.0 | 0.7 | 1.0 | |

**Table 4** Comparison of ADC regarding molecular type

| | ADC | | | | | | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | Min | Max | Mean | SD | Median | Per 25 | Per 75 | |
| *Molecular type* | | | | | | | | |
| A | 1.0 | 1.6 | 1.2 | 0.2 | 1.1 | 1.1 | 1.2 | **0.000** |
| B | 0.5 | 1.4 | 0.9 | 0.1 | 0.9 | 0.8 | 1.0 | |
| HER2 | 0.9 | 1.0 | 0.9 | 0.1 | 0.9 | 0.9 | 0.9 | |
| TN | 0.6 | 1.0 | 0.8ara> | 0.1 | 0.8 | 0.7 | 0.9 | |

Bold = Statistically significant

**Table 5** Pairwise comparison of ADC regarding molecular type

| | A | B | HER2 |
|---|---|---|---|
| B | **0.000** | | |
| HER2 | **0.018** | 1.000 | |
| TN | **0.000** | 0.468 | 1.000 |

Bold = Statistically significant

ADC value measuring $0.8 \times 10^{-3}mm^2/s$. It is postulated that TNBC shows higher ADC values due to necrotic tissue.

In previous studies, breast carcinomas showing high expression of Ki 67 had lower ADC values as opposed to tumors with low Ki 67 expression (26). In breast cancer, an insignificant correlation between both was found. Thus, ADC cannot be used as a prolif-

**Table 6** ROC curve analysis in differentiating molecular type A through ADC value

| AUC | 95%CI | *P* value | Cutoff | Sen | Spec | PPV | NPV | Acc |
|---|---|---|---|---|---|---|---|---|
| 0.964 | 0.914–1.000 | 0.000 | ≥ 1.0 | 100% | 95.6% | 83.3% | 100% | 96.4% |

**Table 7** Comparison of Ki67 regarding grade

| | Ki67 | | | | | | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | Min | Max | Mean | SD | Median | Per 25 | Per 75 | |
| *Grade* | | | | | | | | |
| Grade I | 6.0 | 65.0 | 41.3 | 18.2 | 49.0 | 25.0 | 51.0 | 0.096 |
| Grade II | 10.0 | 80.0 | 40.9 | 16.2 | 49.0 | 30.0 | 50.0 | |
| Grade III | 49.0 | 92.5 | 58.8 | 17.2 | 50.5 | 49.0 | 61.0 | |

**Table 8** Comparison of Ki67 regarding molecular type

| | Ki67 | | | | | | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | Min | Max | Mean | SD | Median | Per 25 | Per 75 | |
| *Molecular type* | | | | | | | | |
| A | 6.0 | 31.0 | 17.6 | 8.2 | 20.0 | 10.0 | 24.0 | **0.000** |
| B | 12.5 | 92.5 | 47.0 | 13.8 | 49.0 | 40.0 | 50.0 | |
| HER2 | 49.0 | 51.0 | 49.6 | 0.9 | 49.0 | 49.0 | 50.0 | |
| TN | 49.0 | 80.0 | 58.0 | 13.3 | 51.0 | 49.0 | 61.0 | |

Bold = Statistically significant

**Table 9** Correlation between ADC and Ki67 value

| r value | *P* value | $R^2$ value | *P* value |
|---|---|---|---|
| − 0.779 | 0.000 | 0.599 | 0.000 |

*r* value = Pearson correlation coefficient

$R^2$ value = coefficient of determination

eration marker in breast cancer [27]. This differs from our results which showed a good negative correlation between both ADC and Ki-67. Low ADC values were associated with tumors with high Ki-67 expression which is a predictor of proliferation and prognosis. This difference may be attributed to a limited number of

**Table 10** ROC curve analysis in differentiating molecular type A from other molecular types through Ki67 value

| AUC | 95%CI | *P* value | Cutoff | Sen | Spec | PPV | NPV | Acc |
|---|---|---|---|---|---|---|---|---|
| 0.966 | 0.923–1.000 | 0.000 | ≤ 35% | 100% | 86.7% | 62.5% | 100% | 89.1% |

patients, uneven distribution of the variable histological grades, and molecular subtypes.

## Limitations of this study

The limited number of patients might have affected our results, especially that all our patients were pathologically proven malignant breast lesions. No cutoff value for luminal subtypes has been elicited during our study result analysis; this might be due to overlap between readings among molecular subtypes. Further studies on a larger scale of patients should be encouraged.

## Conclusions

There was a significant inverse correlation between ADC values and Ki-67 expression. ADC values could be a good discriminator between tumors of molecular subtype A from other subtypes. Ki 67 could also be a good discriminator between tumors of molecular subtype A from other subtypes. Both ADC values and Ki- 67 did not show a correlation with the pathological grade of the tumor.

#### Abbreviations

ADC: Apparent diffusion coefficient; BC: Breast cancer; DWI: Diffusion-weighted imaging; ER: Estrogen receptors; HR: Hormone receptor; MRI: Magnetic resonance imaging; NOS: Non-otherwise specified; NST: No specific type; NEC: Neuroendocrine carcinoid; PR: Progesterone receptors; TNBC: Triple-negative breast cancer.

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#### Author contributions

RH and HA made equal sharing in data collection and analysis; RH made the initial manuscript writing; and HA was involved in editing and adding. Both RH and HA shared data analysis. Both RH and HA shared in writing, editing, and revising data and manuscript. HA performed statistical analysis and impact on results and discussion. Both authors have read and approved the final manuscript.

#### Funding

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#### Availability of data and materials

All data and materials used in this research are available.

## Declarations

#### Ethics approval and consent to participate

The study protocol was approved by the Local Ethics Committee. Vancouver ethical standards were followed in the conduct of the study. Ethics committee reference number is not available. All patients signed a written consent to perform the procedure.

#### Consent for publication

All patients included in this research gave written informed consent to publish the data contained and/or analyzed within this study.

#### Competing interests

The authors declare that they have no competing interests.

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