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Can diffusion-weighted imaging predict tumor grade and expression of Ki-67 in breast cancer? A multicenter analysis

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Abstract

Background: Numerous studies have analyzed associations between apparent diffusion coefficient (ADC) and histopathological features such as Ki-67 proliferation index in breast cancer (BC), with mixed results. The purpose of this study was to perform a multicenter analysis to determine relationships between ADC and expression of Ki-67 and tumor grade in BC.

Methods: For this study, data from six centers were acquired. The sample comprises 870 patients (all female; mean age, 52.6 ± 10.8 years). In every case, breast magnetic resonance imaging with diffusion-weighted imaging was performed. The comparison of ADC values in groups was performed by Mann-Whitney *U* test where the *p* values are adjusted for multiple testing (Bonferroni correction). The association between ADC and Ki-67 values was calculated by Spearman's rank correlation coefficient. Sensitivity, specificity, negative and positive predictive values, accuracy, and AUC were calculated for the diagnostic procedures. ADC thresholds were chosen to maximize the Youden index.

Results: Overall, data of 870 patients were acquired for this study. The mean ADC value of the tumors was $0.98 \pm 0.22 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. ROC analysis showed that it is impossible to differentiate high/moderate grade tumors from grade 1 lesions using ADC values. Youden index identified a threshold ADC value of 1.03 with a sensitivity of 56.2% and specificity of 67.9%. The positive predictive value was 18.2%, and the negative predictive value was 92.4%. The level of the Ki-67 proliferation index was available for 845 patients. The mean value was $12.33 \pm 21.77\%$. ADC correlated with weak statistical significant with expression of Ki-67 ($p = -0.202$, $p < 0.001$). ROC analysis was performed to distinguish tumors with high proliferative potential from tumors with low expression of Ki-67 using ADC values. Youden index identified a threshold ADC value of 0.91 (sensitivity 64%, specificity 50%, positive predictive value 67.7%, negative predictive value 45.0%).

Conclusions: ADC cannot be used as a surrogate marker for proliferation activity and/or for tumor grade in breast cancer.

Keywords: Breast cancer, ADC, DWI, Ki-67

Background

Breast cancer (BC) is the most common noncutaneous malignancy among women, representing four in ten female cancer survivors in the United States [1]. Different imaging modalities such as mammography, ultrasound, and magnetic resonance imaging (MRI) play an essential role in the diagnosis and local staging of BC. According to the

literature, imaging not only can document breast lesions but also can predict histopathological features of BC [2–5]. For instance, Seo et al. reported that the human epidermal growth factor receptor 2 (HER2)-positive subtype of BC was associated with a higher BI-RADS (Breast Imaging Reporting and Data System) category [2]. Some authors also indicated that several imaging features can provide information about proliferation potential or expression of Ki-67 in BC [5]. Szabo et al. reported that rim enhancement on dynamic MRI was associated with high expression of Ki-67 and poor prognosis of BC [5]. Furthermore,

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numerous studies analyzed associations between diffusion-weighted imaging (DWI) and histopathological features in BC, including associations between apparent diffusion coefficient (ADC) and expression of Ki-67 [4, 6, 7]. However, the reported data were mixed. Whereas some authors found significant correlations between ADC and Ki-67 in BC, other did not [8–13]. For example, Li et al. observed a moderate statistically significant correlation between ADC and Ki-67 ($r = -0.566$, $p = 0.025$) [8]. Similar results were also reported by Mori et al. [9]. These authors suggested that ADC would be practical to use for estimating the Ki-67 labeling index [9]. However, Aydin et al. could find only a weak negative correlation between ADC and Ki-67-values in BC ($r = -0.279$; $p = 0.029$) [10]. Finally, some authors did not identify statistically significant correlations between these parameters [11–13]. Similarly, data about relationships between tumor grade and ADC were also inconsistent. These facts question the possibility to use ADC as a surrogate marker for proliferation activity in BC in clinical practice. The purpose of the present study was to provide evidence-based data regarding associations between ADC and expression of Ki-67 as well tumor grade in BC.

Methods

Data acquisition and patients

For this study, the MEDLINE library was screened for associations between ADC and Ki-67 in BC up to December 2017. The following search words were used: “DWI or diffusion weighted imaging or diffusion-weighted imaging or ADC or apparent diffusion coefficient AND Ki-67 OR KI67 OR ki67 OR ki-67 OR mitotic index OR proliferation index OR MIB 1 OR MIB-1 OR mitosis index AND breast cancer OR breast carcinoma.” Overall, 41 items were identified.

In the next step, corresponding authors of all identified reports were contacted via email with a request to provide the data of the investigated patients, including the following for every case: age, precise histopathological diagnosis, tumor grade, mean ADC values, and Ki-67 index. Overall, six of them provided their data [14–19]. Data were provided from the following centers:

- Department of Medical and Biological Sciences, Institute of Diagnostic Radiology, Azienda Ospedaliero Universitaria Santa Maria della Misericordia, University of Udine, Udine, Italy (center 1)
- Department of Radiology, Soon Chun Hyang University Hospital, Seoul, Republic of Korea (center 2)
- Institute of Biomedical Engineering and Instrumentation, Hangzhou Dianzi University, Hangzhou, China (center 3)
- Unit of Radiology, Cancer Institute, Institute for Cancer Research and Treatment of Candiolo (IRCC), Turin, Italy (center 4)
- Department of Radiology, University of Washington, Seattle, WA, USA (center 5)
- Department of Radiology, Pusan National University Hospital, Pusan National University School of Medicine and Medical Research Institute, Busan, Republic of Korea (center 6)

The acquired sample comprises 870 patients (all female; mean age, 52.6 ± 10.8 years; median age, 52 years; range, 24–85 years). The patients had a variety of breast tumor histologic types (Table 1). In every case, breast MRI with DWI was performed with a clinical scanner (1.5 and 3.0 T) with dedicated breast radiofrequency coils. MRI equipment and imaging protocols varied across centers (Table 2).

Statistical analysis

Continuous variables were described by mean value, median value, and SD. Categorical variables were given as relative frequencies. The comparison of ADC values in groups was performed by Mann-Whitney *U* tests where the *p* values are adjusted for multiple testing (Bonferroni correction). The association between ADC and Ki-67 values was calculated by Spearman’s rank correlation coefficient. Sensitivity, specificity, negative and positive predictive values, accuracy, and AUC were calculated for the diagnostic procedures. ADC thresholds were chosen to maximize the Youden index.

Results

ADC values and tumor grade/subtypes

Overall, data of 870 patients were acquired for this study. The majority of tumors were invasive ductal carcinoma (IDC; 81.95%), with a limited number of other subtypes (Table 1). The mean ADC value ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) of the tumors was 0.98 ± 0.22 ; the median value was 0.95; and the range was 0.41–2.18. Ductal carcinoma in situ (DCIS) showed statistically significant higher ADC values ($1.11 \pm 0.24 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) than IDC ($0.97 \pm 0.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$; $P = 0.001$) and invasive lobular carcinoma

Table 1 Analyzed tumors

Diagnosis	No.	%
DCIS	45	5.17
IDC	713	81.95
ILC	57	6.55
Combined IDC/ILC	9	1.03
Mucinous carcinoma	7	0.81
Tubular carcinoma	3	0.35
Metaplastic carcinoma	2	0.23
Unspecified	34	3.91
Total	870	100

Abbreviations: DCIS Ductal carcinoma in situ, IDC Invasive ductal carcinoma, ILC Invasive lobular carcinoma

Table 2 Patients and magnetic resonance imaging techniques

Centers	No. of patients	MRI equipment and field strength	DWI sequences and b-values
1	115	1.5-T scanner (MAGNETOM Avanto; Siemens Medical Systems, Erlangen, Germany)	Single-shot echo-planar sequence (TR/TE: 7100/84 ms); b-values: 0–1000 s/mm ²
2	335	1.5-T scanner (Sonata; Siemens Medical Systems, Erlangen, Germany)	Single-shot echo-planar sequence (TR/TE: 5000/110 ms); b-values: 0–1000 s/mm ²
3	82	3.0-T scanner (MAGNETOM Verio, Siemens Medical Systems, Erlangen, Germany)	Single-shot echo-planar sequence (TR/TE: 7000/85 ms); b-values: 50–1000 s/mm ²
4	143	1.5-T scanner (GE Healthcare Life Sciences, Milwaukee, WI, USA)	Single-shot echo-planar sequence (TR/TE: 7000/85 ms); b-values: 0–900 s/mm ²
5	107	3-T scanner (Achieva TX; Philips Healthcare, Best, The Netherlands)	Single-shot echo-planar sequence (TR/TE: 5336/ 61 ms); b-values: 0–800 s/mm ²
6	88	3-T scanner (Trio Tim; Siemens Medical Systems, Erlangen, Germany)	Single-shot echo-planar sequence (TR/TE: 6600/91 ms); b-values: 0–1000 s/mm ²

Abbreviations: MRI Magnetic resonance imaging, DWI Diffusion-weighted imaging, TR Repetition time, TE Echo time

(ILC; $1.01 \pm 0.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$; $P = 0.044$). There were no significant differences in ADC values between IDC and ILC (Fig. 1). Furthermore, ADC values differed between tumor grades. Grade 1 tumors had significantly higher ADC values ($1.09 \pm 0.27 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) than grade 2 ($0.97 \pm 0.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, $P < 0.001$) and grade 3 ($0.95 \pm 0.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, $P < 0.001$) lesions. No significant differences in ADC values were observed between grades 2 and 3 tumors ($P = 1.00$) (Fig. 2).

Next, ROC analysis was performed to differentiate high/moderate grade tumors from grade 1 lesions using ADC values. Youden index identified a threshold ADC value of 1.03 with a sensitivity of 56.2% and specificity of 67.9%. The positive predictive value was 18.2%, and the negative predictive value was 92.4%. ROC analysis (Fig. 3) showed that the AUC was 0.657.

ADC values and Ki-67 level

The level of the Ki-67 proliferation index was available for 845 patients. The mean value was $12.33 \pm 21.77\%$; the median value was 30%; and the range was 1–100%. ADC correlated weakly with expression of Ki-67 ($p = -0.202$, $P < 0.001$) (Fig. 4). Furthermore, ADC correlated with Ki-67 in the IDC subgroup ($p = -0.173$, $P < 0.001$) and the ILC subgroup ($p = -0.296$, $P = 0.037$), but not in the DCIS subgroup ($p = 0.027$, $P = 0.859$).

A Ki-67 value of 25% was used as the threshold for discriminating between tumors with low Ki-67 expression (< 25%) and high Ki-67 expression ($\geq 25\%$). Tumors with low expression of Ki-67 ($n = 528$ [62.49%]) had higher ADC values than tumors with high expression of Ki-67 ($n = 317$ [37.51%]) ($0.99 \pm 0.22 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ vs $0.95 \pm 0.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, respectively; $P = 0.005$). However, ADC values of the subgroups overlapped significantly (Fig. 5).

In the next step, ROC analysis was performed to distinguish tumors with high proliferative potential from tumors with low expression of Ki-67 using ADC values. Youden index identified a threshold ADC value of 0.91. Using this threshold resulted in sensitivity of 64% and specificity of 50%. The positive predictive value was 67.7%, the negative predictive value was 45.0%, and the AUC was 0.574 (Fig. 6). Other threshold values of Ki-67 were also analyzed (see Table 3).

Discussion

This is the first multicenter study about relationships between ADC and histopathological features such as expression of Ki-67 and tumor grade in BC. Overall, it addresses a key question of whether imaging parameters can reflect clinically relevant histopathological findings. If so, then imaging, in particular ADC values, can be used as surrogate markers for tumor biology in BC.

Table 3 Results of ROC analysis

Ki-67 expression threshold	ADC threshold	Sensitivity	Specificity	AUC	Positive predictive value	Negative predictive value
$\geq 10\%$	0.951	0.704	0.542	0.644	0.267	0.885
$\geq 20\%$	0.913	0.700	0.494	0.613	0.498	0.696
$\geq 30\%$	0.913	0.639	0.512	0.590	0.712	0.430
$\geq 40\%$	0.821	0.808	0.366	0.576	0.844	0.311
$\geq 50\%$	0.821	0.807	0.413	0.600	0.892	0.263

ADC Apparent diffusion coefficient

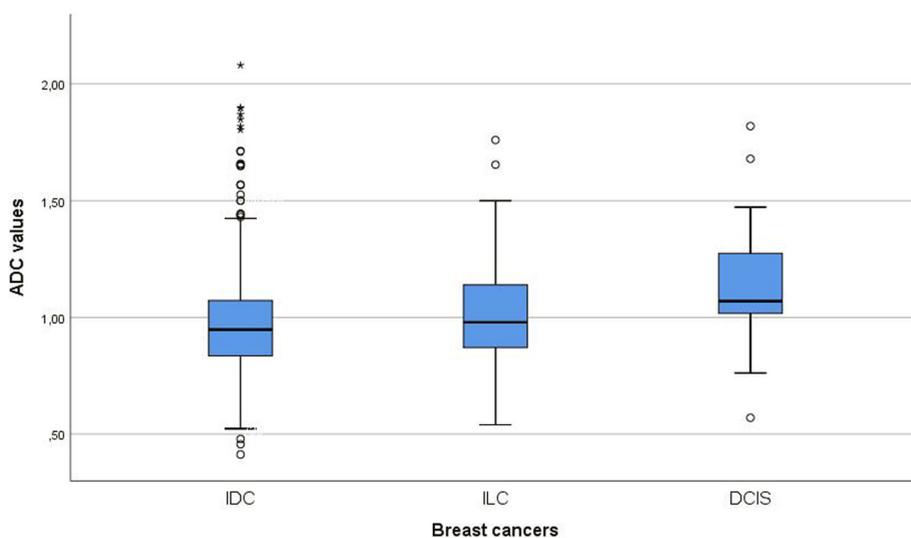


Fig. 1 Comparison of apparent diffusion coefficient (ADC) values between ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC)

Ki-67 is a well-established biomarker in BC [20, 21]. According to the literature, Ki-67 before and after neoadjuvant chemotherapy can predict the prognosis for patients with BC [21]. Furthermore, pretherapeutic Ki-67 is associated with pathological complete response after neoadjuvant chemotherapy in patients with BC [22]. In addition, Ki-67 is associated with overall and disease-free survival of patients with BC [23]. Therefore, it can be important in clinical practice to predict expression of Ki-67 on the basis of imaging.

ADC reflects diffusion of water molecules in tissue [24, 25]. Recently, a meta-analysis identified inverse correlations between ADC and cell count in several malignant

and benign tumors [25]. Furthermore, it has been shown that ADC was associated with expression of Ki-67 in different lesions [26]. Several mechanisms may explain this association. Ki-67 is a nonhistone nuclear protein synthesized throughout the whole cell cycle except the G₀ phase [27, 28]. Cytoplasmic proteins and cytoplasmic viscosity increase during mitosis [29]. These factors may influence water diffusion and ADC. Additionally, water diffusion may be affected by intracellular mitotic membranes.

As mentioned above, numerous prior studies investigated the role of ADC values in BC diagnosis and treatment. However, the reported results regarding associations between ADC and histopathology were

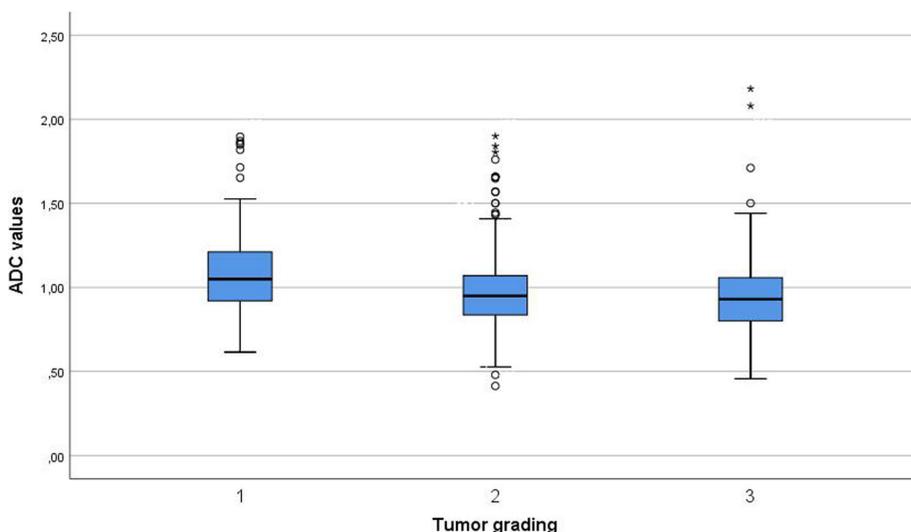
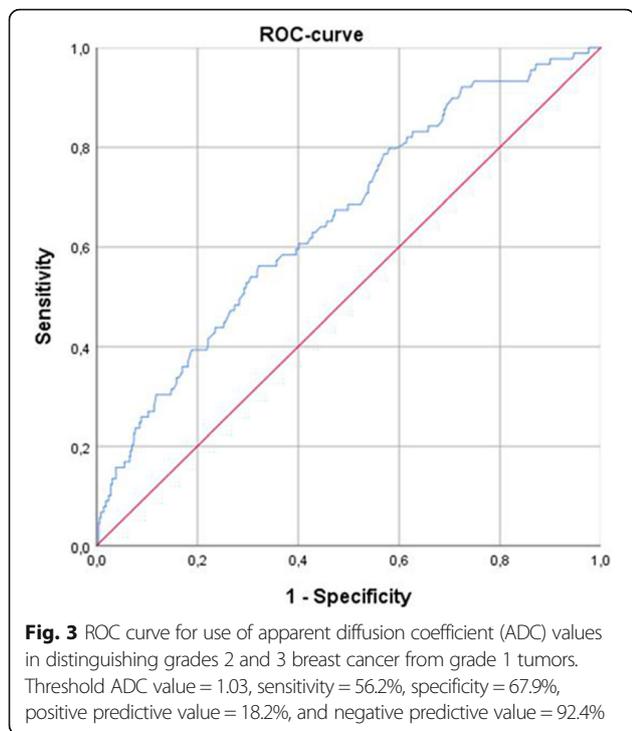


Fig. 2 Comparison of apparent diffusion coefficient (ADC) values between grades 1, 2, and 3 tumors

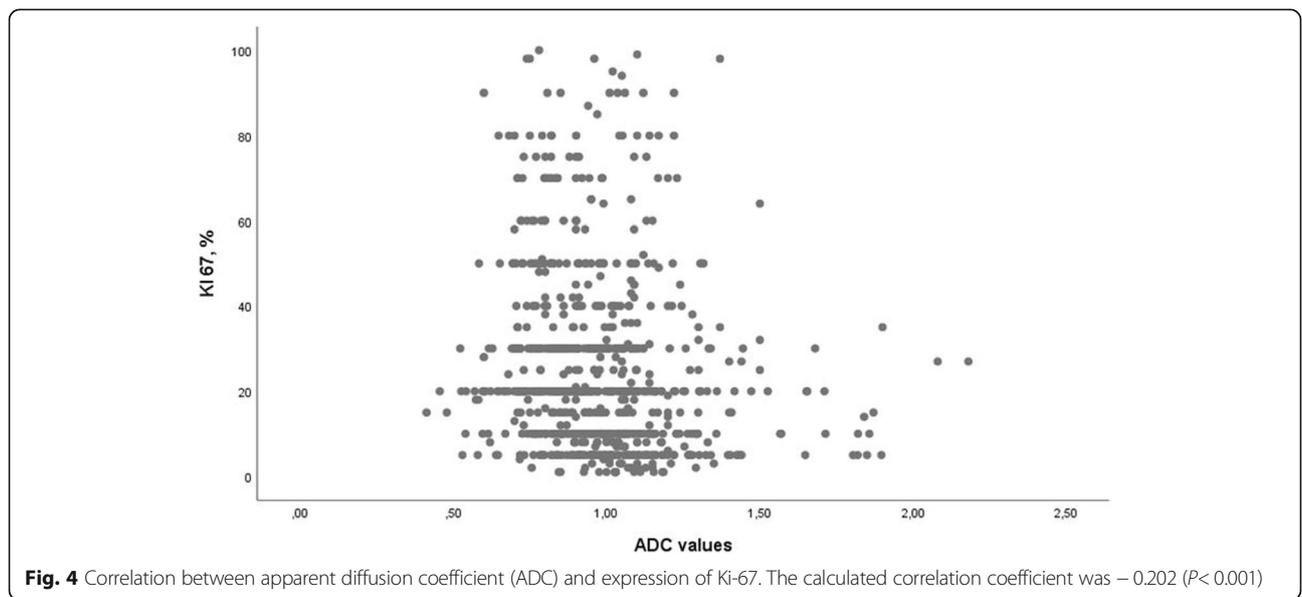


inconclusive. Interpretation of prior results is complicated by differences in study design and analysis. The published radiological studies used different values of Ki-67 expression to discriminate tumors with low and high proliferative activity. For example, in the study of Zhuang et al., a Ki-67 level of $\geq 14\%$ was considered to indicate high proliferation, and $< 14\%$ was considered to indicate low proliferation [30]. Some other studies used a threshold value of 20% [15, 16] or defined more than two Ki-67 categories. For example, De Felice et al. categorized Ki-67 expression

as follows: low Ki-67 ($\leq 14\%$), intermediate Ki-67 (15–30%), and high Ki-67 ($\geq 30\%$) [13]. According to the meta-analysis of Petrelli et al., based on data of 64,196 patients, a Ki-67 cutoff $> 25\%$ is associated with a greater risk of death than lower expression rates [31]. Therefore, a reevaluation of the previous studies on associations between ADC and Ki-67 expression was needed.

The present study suggests that ADC cannot be used as a surrogate marker for proliferation activity in BC. In fact, although ADC values between tumors with high expression of Ki-67 ($\geq 25\%$) differed from those with low levels of Ki-67 ($< 25\%$), the calculated specificity and sensitivity were too low. This applied also for several alternative thresholds of Ki-67 expression ranging from 10% to 50%. Similar results were also observed for distinguishing low-grade and intermediate/high-grade tumors. Statistical analysis identified that grade 1 lesions had higher ADC values than grades 2 and 3 tumors. However, the ROC analysis showed that a possible use of ADC for discrimination of tumor grade in BC has very low specificity and sensitivity. Furthermore, we found that DCIS had statistically significant higher ADC values than IDC and ILC. However, ADC values also overlapped also overlapped distinctly in these subtypes. Therefore, use of ADC does not provide specific information regarding tumor biology in BC that can be used reliably in clinical practice.

The present study is the largest to date on this topic, to our knowledge. However, it has some limitations. The involved patients were investigated with use of different MRI equipment with different technical parameters, such as field strength, DWI sequences, and b-values. This may broaden the range of ADC values in the study and may have influenced



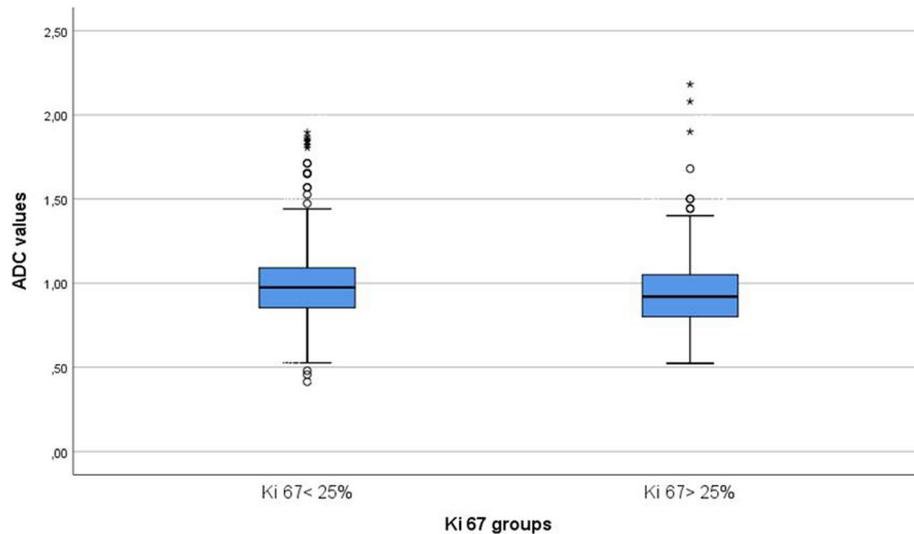


Fig. 5 Comparison of apparent diffusion coefficient (ADC) values between tumors with low expression of Ki-67 (< 25%) and high expression of Ki-67 ($\geq 25\%$)

our results. Furthermore, the patient samples consisted predominantly of only three tumor subgroups, namely DCIS, IDC, and ILC. Our study identified that associations between ADC and Ki-67 were different in several subtypes of BC. Moreover, the calculated correlation coefficients for IDC, DCIS, and ILC in our study differed significantly from those for mucinous carcinoma ($r = 0.035$, $p = 0.892$) reported by Onishi et al. [32]. Presumably, associations between

ADC and Ki-67 or tumor grade may be different in other subtypes of BC such as tubular or medullary carcinomas. However, the included tumors represent the most frequent subtypes of BC, whereas other carcinomas are rarer. We did not analyze possible associations between ADC and other clinically relevant biological features in BC, such as hormonal receptor status and/or HER2 status. This interesting aspect is a goal of further studies.

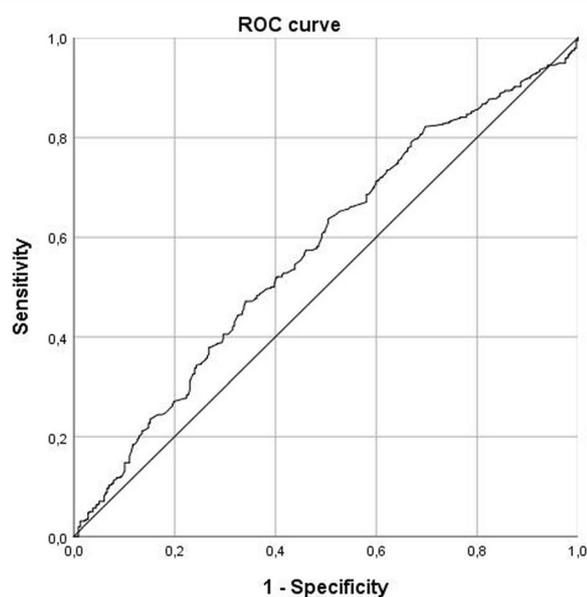


Fig. 6 ROC curve for use of apparent diffusion coefficient (ADC) values in discrimination between tumors with low Ki-67 expression (< 25%) and high Ki-67 expression ($\geq 25\%$). The threshold ADC value was 0.91. Sensitivity = 64.4%, specificity = 50.0%

Conclusions

Our multicenter study shows that ADC cannot be used as a reliable surrogate marker for proliferative activity and/or for tumor grade in BC.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, but restrictions apply to the availability of these data, which were used under license for the present study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the corresponding author (AS).

Authors' contributions

AS made substantial contributions to study conception and design, or acquisition of data, or analysis and interpretation of data. HJM, AW, YWC, LL, LM, SCP, JYK and PC were involved in drafting the manuscript or revising it critically for important intellectual content. HJM, AW, YWC, LL, LM, SCP, JYK and PC gave final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. AS, HJM, AW, YWC, LL, LM, SCP, JYK and PC agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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