J Surg Med. 2023;7(5):319-323.
DOI: 10.28982/josam.7715

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

The efficiency of volumetric apparent diffusion coefficient histogram analysis in breast papillary neoplasms

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Ethics Committee Approval
This study was performed at the University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital. The study protocol (approval number: 2023/35) was approved by the Institutional Review Board on 23.01.2023. Informed written consent was obtained from all patients.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 May 15

Abstract

Background/Aim: Papillary neoplasia encompasses both malignant and benign lesions, and core needle biopsy (CNB) is crucial in their diagnosis. Histological findings determine their management. Here we compare volumetric apparent diffusion coefficient (ADC) histogram analysis of carcinomas and benign pathologies identified by histopathology from excisional biopsies.

Methods: This retrospective study included 524 patients who underwent breast magnetic resonance imaging (MRI) for a suspicious breast mass from January 2018 to October 2022. Patients with benign lesions, incompatible ultrasound-guided CNB results with papillary neoplasia, and those with MRI exams insufficient for diagnosis due to motion artifacts were excluded. After applying the exclusion criteria, the study included 48 patients (average aged 61.5 (14.8) years; range, 31 to 72 years). After excisional biopsies, 30 benign lesions and 18 carcinomas were identified. MRI was acquired at 1.5 T (Verio; Siemens Medical Solutions, Erlangen, Germany), and the b-values for diffusion-weighted imaging were calculated at 1000 s/mm^2. Histogram parameters were computed. Receiver operating characteristic (ROC) curve analysis was performed to investigate diagnostic accuracy, evaluate histogram analysis performance, and determine threshold values.

Results: The ADCmin, ADCmean, ADCmax, and all ADC value percentiles were significantly lower in the carcinoma group than in the benign group (P<0.001). The variance, skewness, and kurtosis were higher in the carcinoma group. ADCmax had the highest area under the curve (AUC: 0.985; cut-off 1.247 × 10^{-3} mm^2/s; sensitivity 86%, and specificity 92%), followed by ADCmean (AUC: 0.950; cut-off 0.903 × 10^{-3} mm^2/s; sensitivity 94%, and specificity 96%).

Conclusion: Volumetric ADC histogram analysis of papillary neoplasia at higher b-values can be an imaging marker to detect carcinoma and quantitatively reveal the lesions' diffusion characteristics.

Keywords: apparent diffusion coefficient, magnetic resonance imaging, papillary neoplasia, volumetric histogram analysis

How to cite: Nalbant MO, Gemici AA, Karadag M, Inci E. The efficiency of volumetric apparent diffusion coefficient histogram analysis in breast papillary neoplasms. J Surg Med. 2023;7(5):319-323.

Introduction

Lesions with unknown malignant potential, or B3 lesions, include papillary neoplasia of the breast and other tumors such as flat epithelial atypia, radial scars, lobular intraepithelial neoplasia, and phyllodes tumors [1,2]. These lesions are found in 3 to 17% of cases, and their detection rate increases with sensitive imaging modalities such as MRI. Ultrasound-guided core needle biopsy is essential for identifying these lesions, but an association with the acquired images is crucial for determining the generalizability of the sample [3-6].

Dynamic contrast-enhanced (DCE) MRI is useful for identifying B3 lesions with less characteristic morphodynamic presentations, reducing the incidence of misdiagnosis and unnecessary procedures. However, some B3 lesions may not be detected by imaging, especially those that are incidental or limited to the periphery of higher-grade lesions [6,7].

Diffusion-weighted imaging (DWI) is a non-contrast MRI method that evaluates the tissue's capability to diffuse fluids. The apparent diffusion coefficient (ADC) can differentiate benign from malignant breast tumors, with malignant lesions showing much lower ADC values due to increased cellularity. Volumetric ADC histogram analysis is used to examine the entire range of ADC parameters, eliminating ROI selection bias and ensuring computation accuracy and repeatability [8-12].

This study compares volumetric ADC histogram analysis between patients with excisional biopsy-confirmed carcinoma and those with benign lesions in papillary neoplasia. To our knowledge, no study has been conducted on volumetric ADC histogram analysis in cases with papillary neoplasia.

Materials and methods

This retrospective case-control study was conducted at the Bakirkoy Dr. Sadi Konuk Training and Research Hospital of the University of Health Sciences. The study protocol (approval number: 2023/35) was approved by the Institutional Review Board on January 23, 2023. Written informed consent was obtained from all participants, and the study was conducted following the Helsinki Declaration guidelines.

This retrospective case-control study included patients who had undergone breast MRI exams within a month before surgery between January 2018 and October 2022 and were diagnosed with either carcinomas or benign lesions through excisional biopsy. The study's inclusion criteria were: (a) patients diagnosed with papillary neoplasia with biopsy; (b) patients who underwent preoperative breast MRIs (including DWI and ADC sequences); (c) patients with histologically confirmed carcinoma or benign lesion with excisional biopsies.

The search yielded 524 patients who underwent breast MRI for a suspicious breast mass. We excluded 253 patients with benign lesions, 211 patients whose ultrasound-guided CNB was incompatible with papillary neoplasia, and 12 patients with poor image quality due to artifacts. Ultimately, our study included 18 patients with histologically confirmed carcinoma and 30 patients with histologically confirmed benign lesions (17 patients with intraductal papilloma, six patients with intraductal papillomatosis, four patients with lobular intraepithelial neoplasia, and three patients with sclerosing adenosis with apocrine metaplasia. Every result was reported with a 95% confidence interval (CI).

A 1.5-T MR system (Verio; Siemens Medical Solutions, Erlangen, Germany) equipped with a 32-channel phased array surface coil for signal reception was used to perform MRI. The diffusion-weighted sequence was administered at b-values of 1000 s/mm². The conventional sequence, matrix 256 × 144, the field of vision (FOV) 250 × 250 mm, the layer thickness 4 mm, the layer spacing 4 mm; the axial turbo inversion recovery magnitude (TIRM), the repeat time (TR) 3500 ms, the echo time (TE) 70 ms; the axial T1-weighted image (T1WI), TR 6 ms, TE 2,5 ms; the axial dispersion weighted image (DWI) sequence, TR 6000 ms, TE 74 ms, B value 1000 s/mm^2, matrix 160 × 160, FOV 250 × 200 mm, layer thickness 4 mm, layer spacing 4 mm.

Image analysis

The DWI raw data were transferred from the picture archiving and communication system (PACS) to a personal computer and processed using the open-source LIFEx 7.2.0 voxel program (https://lifesoft.org). A radiologist with 14 years of experience in breast MRI separately reviewed all MR images and drew each ROI manually to include the lesions. Each ROI was then merged into a volumetric ROI containing voxel data for the entire region, and a volumetric ADC map was generated. The ADCmin, ADCmean, ADCmax, skewness, kurtosis, variance, and percentiles of ADC values were determined. The nth percentile on the histogram represented where n percent of the voxel values were detected on the left. A positive skewness indicated that the right tail was flatter or longer than the left tail, while high kurtosis was characterized by a prominent peak near the mean, a sharp decrease, and long tails. The radiologist was blinded to the clinical data and independently assessed each scan.

Statistical analysis

Statistical analysis was performed using IBM SPSS 23.0 (Chicago, IL, United States). The ADC values of each patient were merged to generate a dataset, and histograms were generated for each group. Histograms revealed variation in the distribution of all measures. Descriptive statistics, such as mean, minimum, maximum, standard deviation, skewness, kurtosis, and percentiles, were calculated for each patient group using individual data, and changes in these descriptive statistics were visually represented. The t-test for independent samples was used to investigate whether these individual statistics differed between groups. ROC curves were created based on individual data, and a threshold value was computed for the acquired statistics. Sensitivity and specificity values for threshold values were then calculated. *P*-values <0.05 were considered statistically significant.

Results

Demographic Data

The study included 48 patients, with a mean age (SD) of 61.5 (14.8) years, ranging from 31 to 72 years. The carcinoma group included 18 cases (Figure 1), while the benign group included 30 cases (Figures 2 and 3). There was no significant difference in age between the two groups (*P*=0.61).

Figure 1: A 72-year-old patient with pathology on surgical excision confirmed papillary carcinoma. The T1W image (a) reveals an irregularly circumscribed hypointense lesion. Turbo inversion recovery magnitude (TIRM) (b) and diffusion-weighted (c) sequences show high signal intensity (c). Manually drawn ROI on the ADC map for assessing the volumetric histogram analysis can be seen (d).

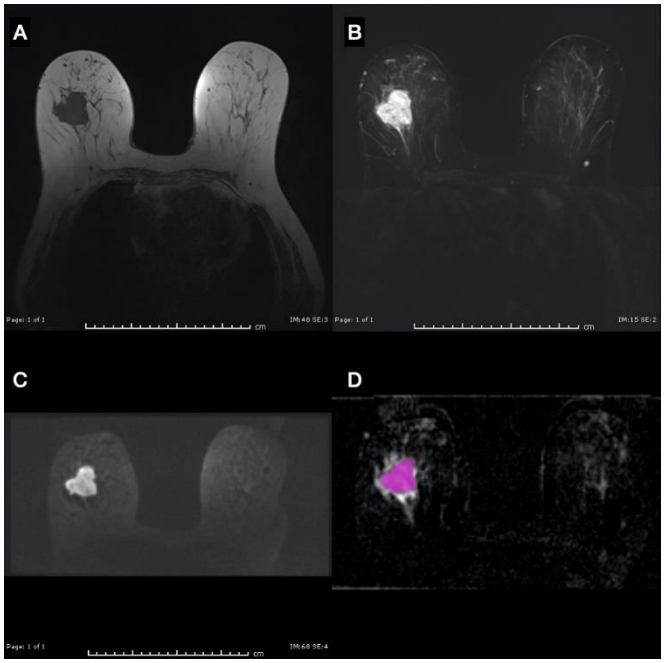


Figure 2: A 44-year-old patient with pathology on surgical excision confirmed intraductal papillomatosis. The T1W image (a) depicts a hypointense lesion with regular margins. Turbo inversion recovery magnitude (TIRM) (b) and diffusion-weighted (c) sequences reveal iso to high signal intensity. A manually drawn ROI is displayed on the ADC map for evaluating the volumetric histogram analysis (d).

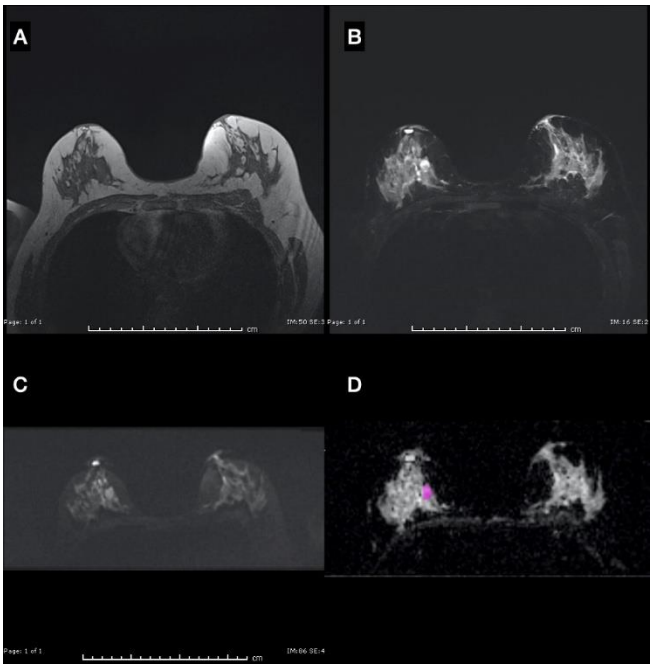
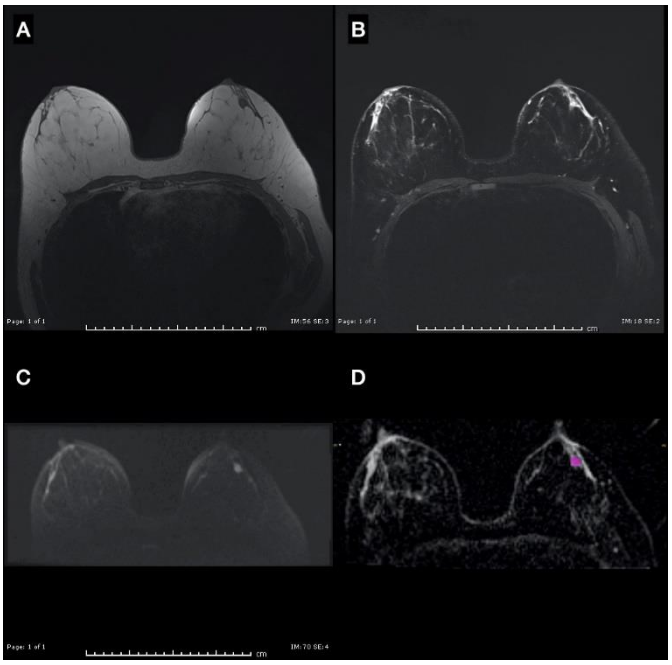


Figure 3: A 42-year-old patient with pathology on surgical excision confirmed sclerosing adenosis with apocrine metaplasia. The T1W image (a) displays a lesion with uniform margins that is hypointense. Turbo inversion recovery magnitude (TIRM) (b) and diffusion-weighted (c) sequences indicate hyperintense lesion. On the ADC map, a manually drawn ROI is shown for assessing the volumetric histogram analysis (d).



Results of ADC histogram parameters in carcinoma and benign group

The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of ADC values, as well as the ADCmin, ADCmean, and ADCmax of the carcinoma group, were all significantly lower (P<0.001) than those of the benign group in the volumetric histogram analysis (Figure 4) (Table 1). In contrast, kurtosis and variance were larger in the carcinoma group than in the benign group (P<0.001), with the difference being statistically significant. Skewness was also larger in the carcinoma group but did not reach statistical significance (P=0.06).

Figure 4: Results of the volumetric ADC histogram analysis of papillary neoplasia. The ADCmean, ADCmin, ADCmax, and 5th–95th percentiles of ADC values of the carcinoma group were all lower than those of the benign group (P<0.001). The variance of the carcinoma group was larger (P<0.05). Apparent diffusion coefficient (ADC) values are expressed as $\times 10^{-3}$ mm²/s.

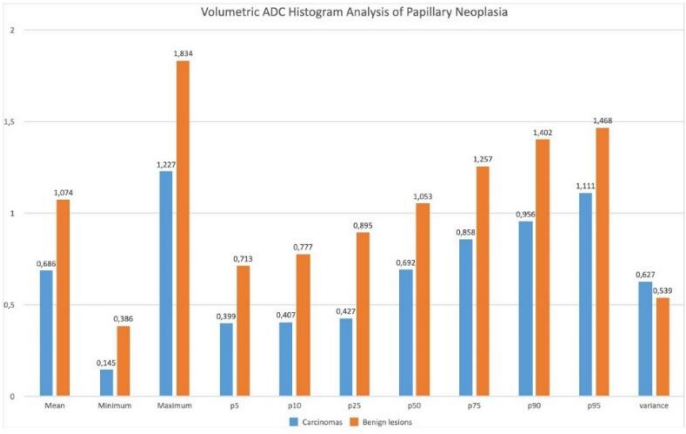


Table 1: Comparisons of ADC histogram parameters between carcinoma group and benign group.

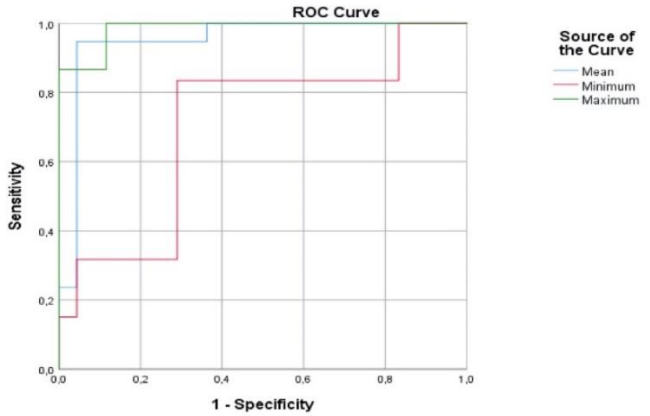
ADC (10^{-3} mm²/s)	Carcinoma group	Benign group	P-value	Significance level
Mean	0.686	1.074	<0.001	99%
Std. Deviation	0.627	0.539	<0.001	99%
Minimum	0.145	0.386	<0.001	99%
Maximum	1.227	1.834	<0.001	99%
Skewness	0.11	0.16	0.06	95%
Kurtosis	0.76	0.21	<0.001	99%
5th	0.399	0.713	<0.001	99%
10th	0.407	0.777	<0.001	99%
25th	0.427	0.895	<0.001	99%
50th	0.692	1.053	<0.001	99%
75th	0.858	1.257	<0.001	99%
90th	0.956	1.402	<0.001	99%
95th	1.111	1.468	<0.001	99%

ADC: apparent diffusion coefficient

Diagnostic performance

The ADCmax had the highest area under the curve (AUC) of 0.985, followed by the ADCmean with an AUC of 0.950, indicating their superior diagnostic effectiveness. Using a cut-off value of 1.247 × 10^{-3} mm^2/s, the ADCmax had a sensitivity of 86% and specificity of 92%. The ADCmean had a threshold of 0.903 × 10^{-3} mm^2/s, with a sensitivity of 94% and specificity of 96%. In contrast, the ADCmin had a lower AUC of 0.716, and a threshold of 0.645 × 10^{-3} mm^2/s yielded a sensitivity of 84% and specificity of 71% (Figure 5).

Figure 5: The ROC (receiver operating characteristic) curve represents the ADCmax, ADCmean, and ADCmin values of the volumetric ADC histogram analysis of papillary neoplasia. The AUC (area under the curve) was 0.985, 0.950, and 0.716, respectively.



Discussion

Here we compared the volumetric ADC histogram analysis of papillary neoplasia between carcinoma and benign groups based on histopathological results from excisional biopsies.

ADC parameters reflect the tumor microenvironment, including membrane stability, extracellular matrix, and cellular proliferation, and are related to the Brownian motion of fluids [13–15]. The signal attenuation due to diffusion is linear when b values range between 200 and 1000 s/mm^2, as predicted by Gaussian diffusion. However, when b-values are above 1000 s/mm^2, non-Gaussian diffusion occurs, leading to a proportional decline in the ADC value [16].

ADC histogram analysis can be used to assess the signal intensity range of voxels based on clinically acquired ADC. Histogram features describing statistical interrelationships between adjacent voxels can highlight the diversity of lesions, providing significant benefits for tumor grading or prognosis evaluation [17–21]. This method is also employed in treating a wide range of illnesses unrelated to cancer [22,23].

In some published studies, volumetric ADC histogram analysis has been used to evaluate breast lesions. Researchers have examined the consistency and repeatability of ADC histogram parameters using ADC histogram analysis, concluding that the repeatability of lower histogram percentiles is comparable to that of mean ADC, while the repeatability of ADC-thresholded volumetric measures is currently poor but could improve with the development of ROI techniques [24].

Guo et al. [25] used volumetric ADC histogram analysis to investigate the relationship between histogram characteristics and Ki-67 expression in breast cancers. They found that the most effective were the median (AUC: 0.943) and mean (AUC: 0.930) ADC histogram parameters. ROC analysis showed that skewness and entropy could be used to determine the Ki-67 status.

Tagliati et al. [26] assessed papillary lesions and found a significant difference in the ADC mean values between individuals without atypia or malignant foci and those with atypia or malignant foci. They suggested that an ADCmean value ≤ 1.418 × 10^{-3} mm^2/s could predict the presence of malignant foci within a papillary lesion with 84% sensitivity and 76% specificity.

Another study on the distinction between malignant and benign papillary breast tumors using ADC values found that the mean ADC values of borderline and malignant lesions were significantly lower than those of benign lesions (P<0.05). They proposed a suitable ADC value threshold of 1.00 × 10^{-3} mm^2/s [27].

Several studies have compared ADC values for differentiating benign and malignant breast tumors [28–30], and similar to our findings, the ADC parameters of malignant tumors were lower than those of benign lesions in these studies. However, our study measured ADC values volumetrically to ensure reproducibility and analyzed more parameters, including percentile values.

Limitations

Our study has several limitations and strengths. One of the strengths is that we performed volumetric histogram analysis in papillary neoplasia of the breast, which to our knowledge, has not been done in other studies in the literature. However, one limitation is that we only evaluated the ADC values derived from higher b values. Additionally, our study utilized a retrospective analysis methodology, which could lead to possible bias in patient sampling. Some lesions contained more cystic components than others, potentially leading to sampling bias. Further studies are needed to validate our findings.

Conclusion

Our study demonstrates that volumetric ADC histogram analysis of papillary neoplasia of the breast at higher b values is a promising imaging marker for differentiating between benign and carcinoma lesions. This method can provide objective and quantitative information about the lesions' diffusion parameters and eliminate bias through volumetric measurement. Furthermore, it is a suitable method for preoperative lesion diagnosis without the need for excisional biopsies. Our findings suggest that this technique could be a valuable addition to the diagnostic toolset for breast cancer.

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