

Utility of Diffusion-Weighted MRI with ADC Values in the Characterisation of Endometrial Lesions: A Prospective Cohort Study

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ABSTRACT

Introduction: Endometrial lesions are a diagnostic dilemma for both radiologists, as well as, gynecologists. Characterising these lesions is crucial for effective management. The Apparent Diffusion Coefficient (ADC) reflects the molecular translational movement of water molecules. Malignant tumours, with higher cellularity than benign tumours, exhibit decreased ADC values compared to benign lesions.

Aim: This study aimed to evaluate the diagnostic accuracy of ADC in conjunction with Diffusion-weighted Images (DWI) for differentiating malignant and benign endometrial lesions.

Materials and Methods: A prospective cohort study was conducted at the Outpatient Department (OPD) of Radiodiagnosis at Sri Guru Ram Das Charitable Hospital in Amritsar, Punjab, India. The study spanned one year and seven months, from February 2020 to October 2021. A total of 100 female patients across all age groups with clinically suspected gynecological complaints related to the endometrium were included. Magnetic Resonance Imaging (MRI) was used to examine the patients with endometrial lesions, and the results were compared with histopathology. The ADC values

of benign and malignant lesions were statistically analysed using Student's t-test. Statistical significance was defined as a p-value < 0.05.

Results: The mean age of participants with benign lesions was lower than that of those with malignant lesions (53.47±8.75 years and 60.00±13.93 years, respectively). The 100 individuals were divided into two groups: group I included individuals with benign lesions (58%), and group II comprised patients with malignant lesions (42%). Conventional MRI demonstrated a sensitivity of 86.2%, specificity of 91.8%, Positive Predictive Value (PPV) of 91.6%, and Negative Predictive Value (NPV) of 100% in lesion detection and differentiation. Combining DWI and ADC value mapping at a high b-value (b=800) in MRI significantly increased sensitivity (92.1%), specificity (97.9%), PPV (97.9%), and NPV (92.3%).

Conclusion: The addition of DWI and ADC values to conventional MRI significantly improved the ability to distinguish malignant endometrial lesions from benign ones. However, histopathology remains the gold standard investigation as MRI inference cannot differentiate low-grade endometrial carcinoma from hyperplasia.

Keywords: Apparent diffusion coefficient, Benign, Magnetic resonance imaging, Malignant

INTRODUCTION

Various imaging modalities, such as ultrasonography (Transvaginal Sonography-TVS) and MRI, have been utilized to detect various uterine pathologies, each with its own advantages [1]. In clinical practice, endometrial biopsy and dilatation and curettage are important for diagnosing endometrial lesions. However, these invasive procedures have limitations and may be challenging for certain patients, such as those with cervical stenosis or obesity, limiting their use [2,3]. Endometrial cavity lesions can present as submucosal leiomyomas, polyps, focal adenomyosis, endometrial hyperplasia, endometrial carcinomas, carcinosarcomas, and choriocarcinomas [1]. MRI is a valuable diagnostic tool for evaluating endometrial pathologies. Conventional MRI, including basic T2 and T1-weighted imaging, provides excellent soft-tissue contrast resolution and is sensitive in determining the anatomical origin, shape, composition, and enhancement pattern of these masses, aiding in diagnosis and treatment decisions [4,5]. MRI is also useful for assessing disease extent and staging, such as in carcinomas and myomas [6]. Diffusion-weighted MRI (DWI) is a functional imaging technique that does not require contrast agents. It relies on the movement of water molecules within tissues, leading to distinctive tissue contrast [7,8].

The Apparent Diffusion Coefficient (ADC) reflects the molecular translational movement of water molecules. In environments with restricted mobility, such as cell membranes, ADC decreases due to

increased tumour cellularity or total nuclear area, both of which limit water molecule transport. Malignant tumours, with higher cellularity compared to benign tumours, exhibit decreased ADC values [9]. This study aims to evaluate the diagnostic accuracy of ADC in combination with DWI for distinguishing between malignant and benign endometrial lesions.

MATERIALS AND METHODS

A prospective cohort study was conducted at the Outpatient Department (OPD) of Radiodiagnosis at Sri Guru Ram Das Charitable Hospital in Amritsar, Punjab, India. The study duration was one year and seven months, from February 2020 to October 2021. The study was approved by the Institutional Ethical Committee (IEC) with letter number (patho 96/2020).

Inclusion criteria: All participants referred to the department with clinically suspected gynecological complaints and confirmed endometrial lesions on MRI were included in the study.

Exclusion criteria: Patients with MRI incompatible devices or implants, patients with claustrophobia, and patients without available histopathological examination reports during follow-up were excluded from the study.

Study Procedure

The study included 100 female patients of all age groups presenting with clinically suspected gynecological complaints related to the

endometrium (such as abnormal uterine bleeding, postmenopausal bleeding, and abdominal pain). After obtaining informed written consent and relevant medical history, patients underwent transvaginal sonography (TVS). Patients with endometrial lesions on TVS were further evaluated with pelvic MRI for endometrial evaluation. The final imaging diagnosis was compared with the histopathological diagnosis.

TVS technique: Sonography was performed using a Voluson E8 machine with a wide-band endocavity volume transducer operating at a frequency of 5-9 megahertz.

MRI technique: All patients underwent MRI imaging using a Philips Achieva D-stream 1.5 Tesla MRI system with a sense body coil, in the supine position.

Imaging protocol: T2-weighted turbo spin-echo (TSE) sequences in sagittal, axial, and coronal planes. T1-weighted TSE and T1-weighted fat-suppressed (FS) sequences in the axial plane. Post-contrast T1-weighted FS sequences in axial and sagittal planes. Diffusion-weighted imaging (DWI) in axial and/or sagittal planes. Additional sequences were used as needed. Three orthogonal (Z, Y, and X) directions with b-values of 0, 300-400, and 700-800 mm²/s were applied. Intravenous contrast was used when necessary. The thickness and matrix for each sequence are shown in [Table/Fig-1].

Sequences	TR (ms)	TE (ms)	Thickness/gap	FOV	Matrix	NSA
TSE T2W SAG	3000-4000	90-120	4/1	250	180×256	3
TSE T2W COR	3000-4000	90-120	4/1	300-400	180×256	3
TSE T2W axial	3000-4000	90-120	4/1.5	250	315×512	3
TSE T1W axial	400-600	10-14	4/1.5	250	190×256	3
TSE TIW FS axial	500-700	10-14	4/1.5	250	185×256	3
DWI SAG/axial	4300-4400	80-90	4/1.5	260	88×128	6

[Table/Fig-1]: Magnetic Resonance Imaging (MRI) protocol.

TR: Repetition time; TE: Time to echo; FOV: Field of view; NSA: Number of signal average; SAG: Sagittal; COR: Corneal

Imaging analysis: A senior radiologist with seven years of expertise reviewed the images and analysed endometrial lesions using conventional MRI, DWI, and ADC values. The images were processed using the "Easy Vision" workstation from Philips Medical Systems. The most homogeneous area of the lesion was selected for measurement on T2-weighted images. After co-localisation of the most homogeneous region with the ADC map, a Region of Interest (ROI) was placed in the suspicious area on the ADC value map at a high b-value (b=800), and mean ADC values were obtained. In cases of signal intensity heterogeneity, multiple small, uniform ROIs with a minimum area of 10 mm² and a maximum area of 55 mm² were placed on the ADC map, and the lowest ADC value was subjectively selected. For statistical analysis, the mean ADC values from the area with the lowest ADC values were chosen. Each lesion was classified as benign or malignant based on its characteristics on conventional MRI, DWI, and ADC values. The results were compared with the histopathological diagnosis.

STATISTICAL ANALYSIS

The ADC values of benign and malignant lesions were statistically analysed using the Student's t-test. Statistical significance was defined as a p-value < 0.05. The authors evaluated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) separately for conventional MRI and DWI with ADC for each parameter. The statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software, version 19.0.

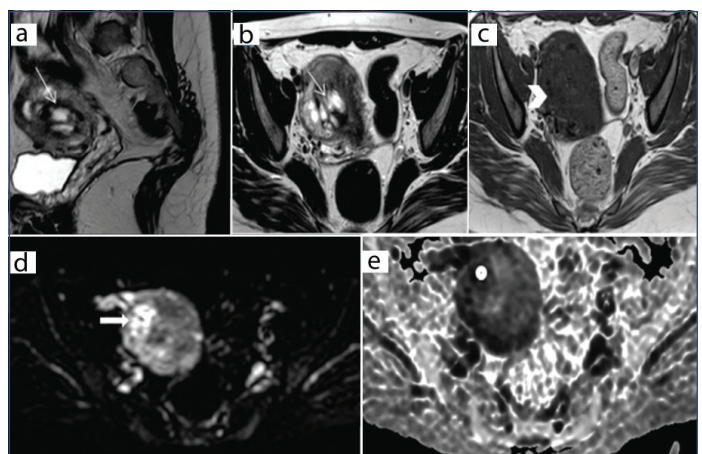
RESULTS

Among the 100 study patients, the majority (68) were in the premenopausal period, while the rest were in the postmenopausal period. The mean age for benign lesions was 53.47±8.75 years, while for malignant lesions it was 60.00±13.93 years. Out of the total patients, 72 suffered from pain, 25 suffered from abnormal bleeding, and 30 suffered from irregular periods. Based on histological findings, the 100 patients were divided into two groups. Group I consisted of 58 (58%) patients with benign lesions, and group II consisted of 42 (42%) patients with malignant lesions [Table/Fig-2].

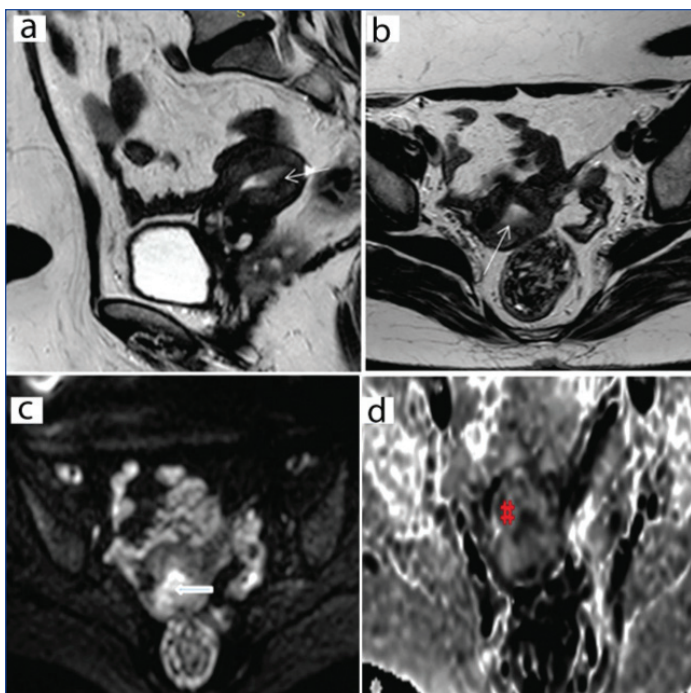
Histopathological diagnosis	No. of patients (n)
Benign lesions	
Endometrial hyperplasia	32
Endometrial polyp	12
Submucosal leiomyoma	10
Focal uterine adenomyosis	4
Malignant lesions	
Endometrial carcinoma	34
Choriocarcinoma	8

[Table/Fig-2]: Distribution of cases on the basis of histopathological diagnosis (N=100).

Regarding the Characterisation of tumours using conventional MRI, there was no statistically significant difference in the T1 signal between malignant and benign uterine tumours (p-value=0.154). However, there was a statistically significant difference in the T2 signal between malignant and benign uterine tumours (p-value=0.01). On T1-weighted images, all lesions, whether malignant or benign, appeared as hypointense or isointense signals [Table/Fig-3a-e]. On T2-weighted images, both benign and malignant lesions showed intermediate to high signal intensity. Choriocarcinoma appeared isointense to hypointense on T1-weighted images relative to normal endometrium, with areas of focal hyperintensity representing areas of hemorrhage. It appeared as a heterogeneous mass beyond the confines of the endometrium due to the loss of normal zonal anatomy with myometrial invasion, as better appreciated on T2-weighted images. Out of the eight cases of choriocarcinoma, six cases had pathology confined to the uterus, while in the other two cases, extension into the parametrium was noted. Endometrial carcinoma presented with heterogeneous thickening of the endometrium on T2-weighted images as seen in [Table/Fig-4a-d].



[Table/Fig-3]: A 28-year-old female with past history of molar pregnancy, presented with complaint of passage of blood clots per vaginum. On MRI evaluation T2 weighted sagittal (a) Axial (b) Shows that, uterus is enlarged due to a poorly defined heterogeneously hyperintense soft tissue lesion occupying endometrial cavity with myometrial extensions. On T1-weighted image (c) Lesion appears isointense and on DWI (d) Shows restriction with low ADC value (0.456 x 10⁻³ mm²/s) (e) Choriocarcinoma.



[Table/Fig-4]: MRI in 48-year-old female on T2WI sagittal (a) Axial (b) Shows ill-defined intermediate signal intensity mass in the endometrial cavity with loss of endo and myometrial interface (white arrow), on DWI (c) Mass shows restricted diffusion with ADC value of $0.47 \times 10^{-3} \text{ mm}^2/\text{s}$ as seen in image (d) On histopathology follow-up, it was proven to be endometrial carcinoma.

On conventional MRI, the sensitivity and specificity were 86.2% and 91.8%, respectively. By combining conventional MRI with DWI and ADC value mapping at a high b-value ($b=800$), the sensitivity and specificity increased to 92.1% and 97.9%, respectively [Table/Fig-5].

Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MRI	86.2	91.8	91.6	100
MRI+DWI	92.1	97.9	97.9	92.3

[Table/Fig-5]: Sensitivity, specificity, PPV, NPV of MRI and MRI+DWI. MRI: Magnetic resonance imaging; DWI: Diffusion-weighted images; PPV: Positive predictive value; NPV: Negative predictive value

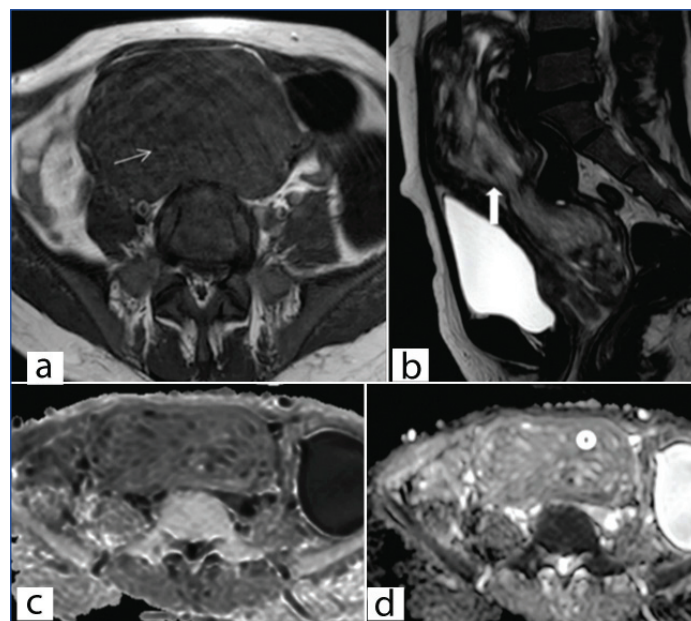
On DWI, free diffusion was noted in benign tumours, while restriction in signal intensity was observed in almost all malignant lesions. The mean standard deviation of ADC values varied significantly between benign endometrial lesions ($1.25 \times 10^{-3} \text{ mm}^2/\text{s}$) and malignant endometrial lesions ($0.925 \times 10^{-3} \text{ mm}^2/\text{s}$), with a p-value of <0.01 .

DISCUSSION

In the present study, the ADC value was found to offer more reliable evidence in differentiating benign endometrial lesions from malignant endometrial lesions compared to conventional MRI sequences. Endometrial hyperplasia is characterised by localised thickening of the endometrium without involvement of surrounding tissues. On T2-weighted images, it also showed intermediate to high signal intensity, similar to endometrial carcinoma. However, on DWI, significant diffusion restriction was observed in cases of malignant lesions due to their larger nuclei, increased cell size, and higher cellularity. As a result, the mean ADC values of malignant lesions were significantly lower, with a mean ADC value of $0.925 \times 10^{-3} \text{ mm}^2/\text{s}$. These findings suggest that the addition of DWI with conventional MRI contributes significantly to differentiating endometrial hyperplasia from endometrial carcinoma. A similar study conducted by Bharwani N et al., also reported increased sensitivity and specificity in diagnosing endometrial lesions (86% and 100%, respectively) when DWI and ADC were added to conventional MRI [10]. The sensitivity and specificity of DWI in endometrial lesions were reported to be 100% and 81%, respectively, in a study conducted by Thomassin-Naggara I et al., [11].

In the present study, one case of histopathologically diagnosed endometrial carcinoma was falsely labeled as endometrial hyperplasia on MRI due to a high ADC value and no restriction on DW images. A study by Fujii S et al., suggested that low-grade tumours have high ADC values [12]. Similarly, Whittaker C et al., described that well-differentiated tumours with low cellularity may show no significant restriction on DW images [13]. In low-grade endometrial carcinoma, such as well-differentiated cases of adenocarcinoma, low cellularity can lead to a significant diagnostic pitfall.

The ADC values of benign lesions were significantly higher than those of malignant lesions, with a mean ADC value of $1.25 \times 10^{-3} \text{ mm}^2/\text{s}$. Endometrial polyps appear as focal masses in the endometrial cavity and show predominantly isointense to slightly hypointense signal intensity relative to the normal endometrium on T2-weighted images [Table/Fig-6a-d]. Endometrial polyps exhibit a hypointense signal on post-contrast T1-weighted images. These polyps are composed of endometrial glands with a thick fibrous or smooth muscle tissue stroma, which may contribute to lower cellularity and increased free water molecule flow, resulting in higher ADC values. Cystic glandular hyperplasia, hemorrhage, and necrosis are commonly observed within the polyps [Table/Fig-6a-d]. Similar findings were reported by El Hafeez M et al., [14]. Submucosal leiomyomas show predominantly isointense to slightly lower signal intensity relative to the normal endometrium on T2-weighted images. They are composed of clusters of smooth muscle cells with a predominant collagen component.



[Table/Fig-6]: A 60-year-old female presented with a complaint of heavy menstrual bleeding. On MRI imaging, the uterus is enlarged, the endometrial cavity is distended, and there is a large, ill-defined mixed signal intensity lesion in the endometrial cavity, extending into the upper part of the cervical canal showing mildly hyperintense signal (arrow) on T2WI (a) Isointense signal on T1WI (thick arrow) (b). On DWI it is not showing any restriction (c) Minimum ADC value was noted to $1.23 \times 10^{-3} \text{ mm}^2/\text{s}$ (taken at the level of white circle) (d) Endometrial polyp with degenerative changes on histopathology.

These features suggest relatively decreased ADC values, similar to polyps. Submucosal leiomyomas can be distinguished from endometrial polyps as they displace or indent the endometrium. In more than half of the cases, leiomyomas show degenerative changes such as hyalinisation and edema [15]. Hyalinisation in leiomyomas leads to a drop in ADC values, while edema can increase ADC values, resulting in varying ADC values based on histological structure. In the present study, both leiomyomas and endometrial polyps showed significantly increased ADC values compared to malignant endometrial lesions [16]. Tamai K et al., have also reported hypointense signals of leiomyomas on both

T1 and T2-weighted images [17]. Submucosal leiomyomas with high ADC levels may resemble other endometrial lesions, including endometrial carcinomas, due to hyperintense signals on T2-weighted images with widespread edema. DWI findings play a crucial role in distinguishing these cases, and leiomyomas with extensive edema have been shown to have higher ADC values compared to malignant lesions [18].

Focal adenomyosis was characterized by an increased thickness of the endomyometrial junctional zone. It revealed an isointense signal intensity relative to normal endometrium on both T1 and T2-weighted images, with some bright patches on T2-weighted images representing cystic regions. On the ADC map, free diffusion with a high signal intensity was observed on DWI [19,20].

DWI was useful in distinguishing between benign and malignant endometrial lesions in the present study. Most benign lesions showed low or iso signal intensity on high b-value images, and their ADC values were relatively high when assessed at a high b-value of $b=800$, ranging from 1.10 to $1.59 \times 10^{-3} \text{ mm}^2/\text{s}$ with a mean ADC value of $1.25 \times 10^{-3} \text{ mm}^2/\text{s}$. Malignant endometrial lesions, on the other hand, exhibited restricted diffusion and had relatively low ADC values when assessed at a high b-value of 800 , ranging from 0.42 to $1.05 \times 10^{-3} \text{ mm}^2/\text{s}$ with a mean ADC value of $0.925 \times 10^{-3} \text{ mm}^2/\text{s}$. These results were consistent with the study by Mansour TMM et al., which reported mean ADC values of $0.95 \pm 0.24 \times 10^{-3} \text{ mm}^2/\text{s}$ for malignant lesions and $1.52 \pm 0.25 \times 10^{-3} \text{ mm}^2/\text{s}$ for benign lesions, showing statistically significant differences [21]. Kececi IS et al., also found a statistically significant reduction in the mean ADC value of malignant lesions ($0.94 \pm 0.18 \times 10^{-3} \text{ mm}^2/\text{s}$) compared to benign lesions ($1.45 \pm 0.22 \times 10^{-3} \text{ mm}^2/\text{s}$) [Table/Fig-7] [10,12,14,21,22].

Year and place of the studies	Aim of study	Results
Bharwani N et al., 2011 Netherland [10]	To assess the use of DWI-MRI in the assessment of tumour grade in endometrial lesions.	Sensitivity 86% and specificity 100%
Fujii S et al., 2007 Japan [12]	To evaluate the diagnostic accuracy of ADC measurement in differentiating malignant from benign uterine endometrial cavity lesions.	Sensitivity, specificity, and accuracy were 84.6%, 100%, and 92%, respectively.
El Hafeez M et al., 2020 Egypt [14]	To detect the role of DWI in assessing uterine neoplasms.	91.7% sensitivity, 100% specificity, and 91.67% accuracy.
Mansour TMM et al., 2019 Egypt [21]	To evaluate the role of DWI in the diagnosis and differential diagnosis of benign and malignant focal endometrial masses.	Conventional MRI sensitivity of 77.27%, specificity of 78.56%, accuracy of 78%, DWI and ADC value sensitivity (95.45%), specificity (92.86%), accuracy (94%),
Kececi IS et al., 2016 Turkey [22]	To evaluate the efficacy of DWI in differentiating between benign and malignant endometrial lesions	Sensitivity 85.7% and specificity 92.8%
Present study	To assess the diagnostic accuracy of ADC in combination with DWI in distinguishing between malignant and benign endometrial lesions, as well as, to describe and localise endometrial lesions on conventional imaging.	On conventional MRI, sensitivity, specificity, were 86.2%, and 91.8%, respectively. Sensitivity, specificity, were raised to 92.1% and 97.9%, respectively, by merging conventional MRI with DWI and ADC value mapping

[Table/Fig-7]: Comparison of various studies regarding the diagnostic value of DWI-MRI in endometrial lesions [10,12,14,21,22].

Limitation(s)

Benign lesions were difficult to monitor by histopathology. Unable to use TVS in unmarried women and cases of cervical carcinoma.

CONCLUSION(S)

Malignant endometrial lesions exhibit much lower ADC values compared to benign endometrial lesions. When combined with DWI, ADC values have shown to be useful in distinguishing between malignant and benign endometrial lesions. The addition of DWI to conventional MRI can be beneficial in the evaluation and differentiation of these lesions in clinical settings. DWI provides increased confidence and consistency in the diagnosis compared to conventional MRI findings, and it should be considered as a necessary component of MRI protocols for evaluating endometrial lesions. However, it is important to note that histopathology remains the gold standard investigation, as MRI findings alone cannot differentiate low-grade endometrial carcinoma from hyperplasia.

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