How to Cite:
Abd Allah, S. S., El Hady, E. said M. A., Gab Allah, G. M., Mahmoud, A. H., & Tawfik, A. M. (2022). Diagnostic Value of Volumetric Histogram- Based Diffusion Analysis in the Differentiation between Benign &Malignant Gynecologic Lesions. *International Journal of Health Sciences*, *6*(S9), 1825–1839. https://doi.org/10.53730/ijhs.v6nS9.12825

Diagnostic Value of Volumetric Histogram- Based Diffusion Analysis in the Differentiation between Benign &Malignant Gynecologic Lesions

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Abstract--- Purpose: To evaluate the diagnostic value of volumetric histogram based diffusion analysis in the differentiation between benign and malignant gynecologic lesions & to compare it with the conventional partial slice mean apparent diffusion coefficient (ADC).

Patients & methods: This is a prospective study included 80 patients with different gynecologic lesions. Fifty one patients had benign lesions & twenty nine patients had pathologically proved malignant lesions. All patients underwent Diffusion Weighted Imaging (DWI) of the pelvis. The images were

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 May 2022, Manuscript revised: 18 July 2022, Accepted for publication: 27 August 2022

evaluated qualitatively by visual assessment, then quantitatively using two different methods. The first method was the volumetric histogram based diffusion analysis (including minimum ADC, maximum ADC, mean ADC, kurtosis & skewness) & the second method was via evaluation of ADC by the conventional single slice method.

Results: There was statistically significant difference between benign and malignant lesions on qualitative DWI assessment (P<0.001). All malignant lesions displayed restricted diffusion. While most of benign lesions exhibited non restricted diffusion (n=35).

The most significant parameters of volumetric histogram were mean & minimum ADC (P= 0.01* & 0.023*), while other parameters were insignificant (P= 0.393, 0.094 & 0,491).When 0,905 & 0.680 x10 -3 mm2/s were used as volumetric mean & minimum ADC cut off values respectively, we achieved 72%, 76% sensitivity, 56.5 %, 54.3% specificity & 62.5%& 61.9% diagnostic accuracy respectively as regard the differentiation between benign and malignant lesions.

There was statistically significant difference between benign & malignant lesions using conventional single slice mean ADC (p value 0.001). When 0.950 x10 -3mm2/s was used as a mean ADC cut off value, it yielded 90.9% sensitivity, 74.6 % specificity & 80% diagnostic accuracy as regard the differentiation between benign and malignant lesions.

When comparing the diagnostic performance of conventional partial slice mean ADC with that of the volumetric histogram based mean ADC, we found that the sensitivity, specificity, PPV, NPV and accuracy of partial slice mean ADC were higher than histogram based mean ADC

Conclusions: Volumetric histogram based mean & minimum ADC analysis can differentiate between benign and malignant gynecologic lesions and it showed a diagnostic performance less than that based on conventional mean ADC.

Keywords: Histogram diffusion metrics, Minimum ADC, maximum ADC, Skewness, Kurtosis, conventional diffusion, magnetic resonance imaging.

Introduction

Gynecologic malignancies comprise five main categories according to their site of origin (from ovaries, fallopian tubes, endometrium, myometrium, cervix, vagina, or vulva). Histologically and epidemiologically, these are extremely different in the age at which they occur, natural history, and survival (1). Imaging is crucial for disease evaluation, determining and optimizing management, assessing response, and identifying recurrence. Nevertheless, pre-surgical evaluation of gynecologic abnormalities by conventional MRI remains challenging (2). This difficulty can be attributed to the variable and potentially overlapping imaging features of a large spectrum of benign and malignant gynecological lesions (3). The innovation of newer functional imaging sequences such as diffusion-weighted (DW) imaging has addressed many of these issues and enhanced the diagnostic

capabilities of MR imaging. The developments have been made possible by recent advances in MR imaging hardware and software (eg, multichannel coils, echo-planar imaging, parallel imaging, higher magnetic field strengths, and stronger gradients), which have resulted in a substantial decrease in scan times (4). DW imaging does not require administration of an exogenous contrast agent and can be used for patients with renal insufficiency (4). As a result of technical developments and recent research, DW imaging has emerged as a promising tool for detecting and characterizing gynecologic tumors, determining the anatomic extent of disease, understanding lesion pathophysiology, predicting and monitoring treatment outcome (5). The quantitative apparent diffusion coefficient (ADC) value is derived from the exponential attenuation of signal intensity (SI) between two or more b values. Apparent diffusion coefficient (ADC) values obtained from diffusion-weighted imaging (DWI) have shown potency in characterizing different pathologies as benign or malignant (6).The ADC measures the random motion of water molecules and decreases with increasing tumor cellularity, as seen in malignant lesions (7). Distribution of ADC values vary within any tumor; therefore, the mean ADC may not represent the full spectrum of histology within a tumor (8).

The whole-lesion histogram-based ADC analysis offers a more comprehensive assessment of a given abnormality than traditional ADC measures and provides an option for quantifying the overall heterogeneity of the tumor. Recently, ADC histogram analysis has been increasingly applied to differentiate the histological types, predict tumor grade, and assess treatment response (9).

Our aim in this study was to evaluate the diagnostic value of volumetric histogram based diffusion analysis in the differentiation between benign and malignant gynecologic lesions & to compare it with the conventional partial slice mean apparent diffusion coefficient (ADC).

Methods

Study population:

This prospective study was performed between February 2020 and February 2022 in the diagnostic radiology department of Mansoura University Hospitals. Patients were referred from the gynecology and obstetrics department as well as from the oncology department. Our study included 80 patients (n= 80) with clinically or sonographically detected gynecological lesions as well as patients with pathologically proven gynecological malignancies who did not receive any treatment, yet. Patients with absolute contraindication for MRI (eg, insertion of aneurysm clips, or coronary, or peripheral artery stents) as well as patients who refused to participate, were all excluded from this study.

MR acquisition:

MRI was performed using a 1.5 T magnet (Ingenia; Philips Medical Systems, Best, Netherlands). Patients lied in a supine position using phased array coils for the abdomino-pelvic studies.

After completion of the conventional MRI sequences, DW imaging was done in the axial plane using a single-shot echo-planar imaging sequence with the following

parameters; repetition time (TR)/ echo time (TE) range 8,002-10,002/70-100, field of view (FOV) 32 - 42 cm., slice thickness 5mm., intersection gap 1 mm., and matrix 128 × 128. The used b values were 0, 500 and 1000 s/mm2.

Post-processing and image interpretation:

Generation of ADC maps for both visual and quantitative analysis was done. The Digital Imaging and Communications in Medicine (DICOM) images were transferred to workstation (extended MR Workspace 2.6.3.5, Philips medical systems Nederland B.V) supplied by the vendor.

Qualitative DWI-MRI assessment;

For all lesions, visual analysis was done, the signal intensity of the lesions on DWI (b1000 mm2/s) was evaluated using the myometrium as internal reference. The lesion was isointense–hypointense if it displayed a signal intensity equal or lower to the myometrium and the lesion was hyperintense if it displayed a signal intensity higher to the myometrium.

The lesions were divided into restricted, non-restricted diffusion, lesions with T2 shine through and black out sign as the following; When the lesion displayed a high SI on DWI (b value 1,000 s/mm2) and low signal on ADC map, it was categorized in the restricted group and when the lesion displayed low SI on DWI (b value 1000 s/mm2) and high on ADC map it was categorized in the non-restricted group, when it displayed high SI on both b 1000 s/mm2 and ADC map it was categorized in the T2 shine through lesions group (non -restricted) and when it had low SI on both b 1000 s/mm2 and ADC map it was categorized in non -restricted black out sign lesions.

Quantitative volumetric histogram- based diffusion analysis:

By outlining the whole lesion in all available cuts, a volumetric histogram based diffusion analysis was automatically calculated; including minimum ADC, maximum ADC, mean ADC, skewness & kurtosis.

Quantitative conventional partial slice mean ADC:

The region of interest (ROI) was put within the most restricted solid portion of the lesion & ADC value was automatically calculated.

Pathological examinations: -

The pathological examination was done for 43 patients (n=43), Twenty nine patients (n=29) had malignant lesions & the remaining fourteen patients (n=14) had benign lesions.

Statistical analysis

Data was analyzed using SPSS (Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Qualitative data were analyzed using number and percent. Quantitative data were analyzed using median (minimum and maximum) for non-normally data and mean, standard deviation for normally data .Significance of the results was done at the (0.05) level. For qualitative data Chi-Square test, Monte Carlo and Fischer exact test for comparison of 2 or more groups were used, for quantitative data between groups: we used Mann-Whitney U test & we used ROC for diagnostic accuracy. We used the curve to obtain sensitivity and specificity, PPV, NPV and diagnostic accuracy.

Results

This study included 80 female patients; the mean age of the studied patients with benign lesions was 43 years versus 61 years for malignant lesion with statistically significant difference between them (p<0.001*).
Patients were divided into two groups the first group included patients with benign gynecologic lesions (n=51 representing 63.7 % of all patients) and the second group included patients with malignant gynecologic lesions (n=29 representing 36.2 % of all patients) [Table (1)].
The most common benign pathology was fibroid (n=19 representing 37.2% of total benign lesions). The most common malignant pathology encountered in the study was cervical squamous carcinoma (n=12 representing 41.3 % of total malignant lesions).

Qualitative DWI assessment (visual assessment)

There was statistically significant difference between benign and malignant lesions on DWI (P<0.001).
ALL malignant gynecologic lesions (n=29) showed restricted diffusion (n=29/29). On the other hand the benign gynecologic lesions showed variable patterns of diffusion: 12 cases (12/51) showed iso intense SI in DWI & ADC map (non-restricted diffusion), 19 lesions showed low SI in both DWI &ADC map (non –restricted black out sign) & 4 cases showed high SI in both DWI & ADC map (non-restricted T2 shine through). Whereas, 16 cases displayed restricted diffusion (n= 16/51)
The use of qualitative DWI in differentiation of benign gynecologic lesions from malignant lesions yielded a 100% sensitivity, 65.1% specificity, 59.6% PPV, 100% NPV and 77% diagnostic accuracy.

Volumetric histogram based- diffusion analysis:

There was statistically significant difference between benign and malignant lesions as regard mean and minimum ADC values (P = 0.01*, 0.023*) and no statistically difference between benign and malignant lesions as regard maximum ADC, kurtosis and skewness [Table (2)].
The cutoff mean & minimum ADC values used to differentiate benign lesions from malignant lesions were 0.905 & 0.680 x 10-3 mm2/s, respectively with AUC of 0.655 &0.653 respectively yielding 72 % & 76% sensitivity, 56.5% & 54.3% specificity and 62.5% & 61.9% diagnostic accuracy, [table (3), figure (1)].

Quantitative assessment (partial slice ADC measurement):

There was statistically significant difference between benign gynecologic lesions and malignant lesions as regard mean ADC values (P < 0.001). The cutoff ADC value used to differentiate benign lesions from malignant lesions was 0.950 x 10−3 mm2/s with AUC of 0.830, yielding 90.9% sensitivity, 74.6% specificity, 80% diagnostic accuracy [table (4,5), figure (2)].
The sensitivity, specificity, PPV, NPV and accuracy of partial slice mean ADC were higher than histogram mean ADC as shown in [Table (6)].

Discussion

MRI has an essential role in different gynecologic lesions from detection to recurrent disease assessment. Functional MRI can aid in establishing a correct diagnosis, however, it is still sometimes essential to do biopsy and histopathological analysis (10).
Our study aimed to highlight the added value of volumetric histogram based diffusion analysis in differentiating benign and malignant gynecologic lesions.

This study included 80 patients; their ages ranged from 23 to 81 years with mean age 46.6 years. The mean age of patients with benign lesions was 43.53Years, and that of patients with malignant lesions was 61.52Years. This correlates with the study done by Otero-García et al., (10) who reported that endometrial carcinoma (EC) usually presents in old age group beyond 50 years old.

Among the 80 patients included in this study, we had 51 benign lesions & 29 malignant lesions, all malignant lesions were pathologically proved. The most common benign lesions was fibroid (N=19) and the most common malignant lesions was cervical carcinoma (N=12) this correlates with Duc and Huy, (11) who concluded that the uterine fibroid is the most common gynecologic tumor.

DW-MRI is a functional imaging technique that does not require exogenous contrast medium administration. Diffusion weighted imaging is becomeing a good diagnostic tool and can provide more information for the differentiation between benign and malignant lesions in different body regions (12).

There was statistically significant difference between benign and malignant lesions on DWI ($P<0.001$). All malignant lesions displayed restricted diffusion. Although the DWI SI was valuable in diagnosing malignant gynecologic lesions, some benign lesions displayed restricted diffusion too (n =16), our results were in line with that of Addley et al., (13).

This difference between DWI and pathological diagnosis could be explained by the presence of dense cellularity, pus & blood which are a fluid with high viscosity. Our results were in accordance with the published research by Demulder and ascher, (14) who found that some benign lesions as inflammatory pelvic lesions and cellular fibroid, displayed restricted diffusion

The use of qualitative DWI was not enough in differentiating benign gynecologic lesions from malignant lesions with 100% sensitivity, 65.1% specificity, 59.6% PPV, 100% NPV and 77% diagnostic accuracy.

In our study, quantitative measurement was done as a complementary tool to the qualitative DWI using two different methods: either by volumetric histogram based diffusion analysis or by conventional partial slice mean ADC to reveal which of the two methods was of higher diagnostic performance.

The evaluation of histogram-based texture metrics on the ADC map has been applied in breast, neurological and abdominopelvic imaging to distinguish benign from malignant tumors, predict tumor grade, and assess treatment response. Therefore, the purpose of our investigation was to assess the utility of histogram-based diffusion metrics.

In our study The ADC based histogram was done for (80) patients, (51) benign & (29) malignant. We found that minimum & mean ADC values were lower in malignant lesions compared to benign lesions with statistically significant difference between them, the denser cellularity in malignant lesions leads to the restriction of water molecular diffusion and corresponding decreased ADC values

The mean ADC value for benign lesion was 1.063 ×10-3 mm2/sec & for malignant lesion was 0.895×10-3 mm2/sec and when (0.905 x 10−3 mm2/s) used as a cutoff ADC value to differentiate benign from malignant lesions, the sensitivity was 72.4 %, specificity 56.8 %, accuracy 62.5% and the AUC 0.655.

The minimum ADC value for benign lesion was 0.774 ×10-3 mm2/sec & for malignant lesion was 0.613×10-3 mm2/sec and when (0.68 x 10−3 mm2/s) used as a cutoff ADC value to differentiate benign from malignant lesions, the sensitivity was 76.0%, specificity 54.3 %, accuracy 61.9% and the AUC 0.653.

This is in agreement with Guan et al. (15) who published that all histogram parameters of cervical cancer were significantly lower than normal cervical tissues & also matching with Kierans et al., (16) who found that mean &minimum ADC parameters were lower in malignant endometrial lesions.

Skewness reflects the asymmetry of the ADC histogram distribution. Positive skewness indicates that most voxels contain ADC values below the mean, and a long tail of the curve leans rightward. Prior studies have demonstrated significantly higher skewness in soft tissue sarcomas than in benign peripheral neurogenic tumors, as well as invasive compared to noninvasive intraductal papillary neoplasms of the bile ducts. Greater ADC skewness in the tumor probably reflects this increased structural heterogeneity within the lesions, with a predominance of lower ADC values indicating the reduction in ADC arising from neoplasia-related cellularity (17).

Despite these great values of the histogram based skewness as a parameter in evaluating the tumor heterogeneity, we found no statistically significant difference between benign & malignant gynecologic lesions in our study as regard skewness & this could be explained by presence of heterogeneous malignant & some benign lesions as well in our study with increased skewness values for both.

As regard the conventional partial slice mean ADC in our study, the mean ADC value of malignant lesions was (0.791x 10−3 mm2/s) which was statistically significantly lower than that of benign lesions (1.05 x 10−3 mm2/s) and when (0.95 x 10−3 mm2/s) used as a cutoff ADC value to differentiate benign from malignant lesions, 16 cases of benign lesions (false positive) were lower than (0.95 x 10−3 mm2/s) while 2 cases malignant lesions (false negative) were higher than this value (range 0.98 - 1.1x x 10−3 mm2/s) yielding 90.9% sensitivity ,74.6% specificity & 80% accuracy, the AUC was 0.830.

The explanation was various cut off ADC values have been used to differentiate malignant from benign lesions. Our results were consistent with Motoshima et al., (30) who published the mean ADC values between the benign and malignant tumors varied significantly. Using a cutoff ADC value of 1×10-3 mm2/sec, discriminating benign from malignant lesions yielding 74% sensitivity, 80% specificity, 94% positive predictive value, and 44% negative predictive value (NPV). The lower ADC value within some benign lesions can be explained by the presence of dense cellularity, pus & blood which are a fluid with high viscosity and this led to decreased ADC readings. Our results were in accordance with the published research by Demulder and ascher, (14).

In our study, when we compared the partial slice mean ADC and volumetric histogram based mean ADC, we found that the sensitivity, specificity, PPV, NPV and accuracy of conventionalpartial slice mean ADC were higher than histogram based mean ADC, this is not similar to the research published by Ozturk et al., (18) & Zhang et al., (17) who reported that the diagnostic performance of histogram mean ADC and partial slice mean ADC were similar.

This could be explained due to technical post processing difference as the partial slice mean ADC was taken within the most solid restricted portion while the ADC based histogram was obtained by outlining the whole lesion including both solid & cystic parts leading to different ADC values.

In addition, we had variable gynecologic pathologies, 22 out of 51 benign lesions with restricted diffusion had lower mean ADC value (<0.905) increasing the number of false positive lesions ,on the other hand we had six neoplastic ovarian lesions with ADC values ranging from (0.93 - 1.2 x10-3 mm2 /sec) more than the

used cuttoff value due to the outlining of both solid & cystic components of the ovarian neoplasm leading to false negative results ,these leaded to decreased sensitivity &specificity of histogram based mean ADC compared to partial slice mean ADC.

Limitations:

This study has some limitations;

Variable gynecologic lesions with Small number of patients in some pathologic categories.

DWI in the pelvis is still limited by technical problems that can affect image quality.

The use of fused T2-WI and high b value imaging with background body signal suppression (DWIBS) can improve anatomic data.

As regard the ADC measurements of the ovarian neoplasm, the selection of the area must be done for solid parts only.

Conclusions

We concluded that volumetric histogram based diffusion metrics could differentiate between benign and malignant gynecologic lesions with less diagnostic performance compared to conventional partial slice mean ADC.

List of abbreviations

ADC: Apparent Diffusion Coefficient; AUC: Area under the curve; CI: Confidence interval; DWI: Diffusion-Weighted Imaging; FSE: Fast Spin Echo; FP: False Positive; FN: False Negative; FOV: Field of view; MRI: Magnetic resonance imaging; ms: Millisecond; mm: Millimeter; MCC: Matthews Correlation Coefficient; NPV: Negative predictive value; PACS: Picture Archiving & Communication System; PPV: Positive predictive value; ROI: Region Of Interest; TR: Repetition time; TP: True Positive; TN: True Negative; TE: Echo time.

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Tables

Table (1): Benign & malignant gynecologic lesions.

Benign lesions (N=51)	**Malignant lesions (N=29)**
Fibroid (19)	Endometrial carcinoma (9)
Adenomyosis (9)	Endometrial sarcoma (2)
Endometrial polyp (4)	Cervical squamous carcinoma (10)
Endometrial hyperplasia (2)	Cervical adenocarcinoma (1)
Endometrioma (10)	Cervical adenosquamous carcinoma (1)
Tubo ovarian abscess (2)	Ovarian serous adenocarcinoma (4)
Dermoid (2)	Ovarian mucinous adenocarcinoma (1)
Simple mesothelial cyst (1)	Granulosa cell carcinoma (1)
Complicated cyst (1)	
Mucinous cystadenoma (1)	

Table (2): Volumetric histogram based diffusion metrics among the studied gynecologic lesions.

	Benign	**Malignant**	**Test of significance**
Mean ADC x 10-3 mm2/s	1.063 (± 0.38)	0.895 (± 0.285)	Z=2.58 P=0.01*
Minimum ADC x 10-3 mm2/s	0.774 (± 0.393)	0.613 (± 0.241)	Z=2.27 P=0.023
Max ADC x 10-3 mm2/s	1.51 (± 0.668	1.37 (± 0.45)	Z=0.854 P=0.393
Kurtosis	4.64 (± 2.56)	3.70 (± 2.17)	Z=1.68 P=0.094
Skewness	0.730 (± 0.706)	0.885 (± 0.635)	Z=0.688 P=0.491

Parameters described as median (range), Z: Mann Whitney U test,*statistically significant

Table (3): Receiver operating curve of volumetric histogram based diffusion metrics in differentiating malignant from benign lesions

	AUC (95%CI)	P-Value	Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
Mean ADC value	0.655 (0.522-0.788)	0.032*	0.905	72.0	56.5	57.4	79.4	62.5
Minimum ADC	0.653 (0.525-0.782)	0.034*	0.680	76.0	54.3	47.5	80.6	61.9
Maximum ADC	0.552 (0.401-0.702)	0.474	1.255	56.0	58.7	42.4	71.8	58.3

AUC: Area Under curve, PPV: positive predictive value, NPV: Negative predictive value.

Table (4): Single slice mean ADC value in the studied gynecologic lesions.

	Benign	Malignant	Test of significance
ADC x 10-3 mm2/s Mean ± SD	1.095 (± 0.315)	0.791 (± 0.244)	Z=5.42 P<0.001*

Z: Mann Whitney U test,*statistically significant

Table (5): Receiver operating curve of single slice mean ADC value in differentiating malignant from benign gynecologic lesions.

	AUC (95%CI)	P-Value	Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
ADC value	0.830 (0.735-0.925)	<0.001*	0.950	90.9	74.6	63.8	94.3	80

AUC: Area Under curve, PPV: positive predictive value, NPV: Negative predictive value.

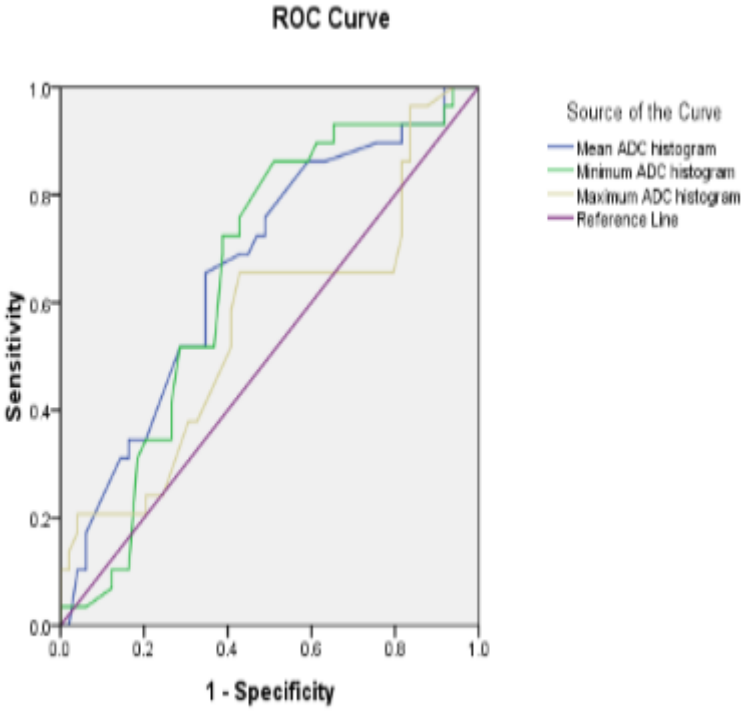
Table (6): Diagnostic performance of volumetric histogram based versus partial slice mean ADC in the studied cases

	Sensitivity	Specificity	PPV	NPV	Accuracy
Partial slice Mean ADC	90.9*	74.6*	63.8*	94.3*	80*
histogram metrics	72	65.5	57.4	79.4	62.5

PPV: positive predictive value, NPV: Negative predictive value.

Figures:

Figure (1): Receiver operating curve for volumetric histogram based diffusion metrics in differentiating malignant from benign gynecologic lesions.
Figure (2): Receiver operating curve for single slice mean ADC value in differentiating malignant from benign gynecologic lesions.
Figure (3): 61- year- old female pathologically proved stage IA endometrial cancer. (A) Sagittal T2WI (B) Axial T2WI showed ill-defined endometrial soft tissue mass of intermediate signal (C)Axial DWI, (D) Axial ADC map showed high endometrial SI on DWI and low signal on ADC map. The mean ADC value = 0.86 x 10-3 mm2/s (restricted diffusion). (E) Whole lesion ADC based histogram showed the following parameters mean ADC 0.8 x10-3, maximum ADC 0.9 x10-3, minimum ADC 0.7x10-3, kurtosis 1.8 & skewness .45.
Figure (4): 65- year- old female pathologically proved benign endometrial polyp (A) Sagittal T2WI (B) Axial T2WI showed well defined endometrial mass of low SI, intact Junctional zone. (C)Axial DWI, (D) Axial ADC map showed low SI on DWI and low signal on ADC map with T2shine through of endometrium. The mean ADC value = 1 x 10-3 mm2/s (non - restricted diffusion, black out sign). (E) Whole lesion ADC based histogram showed the following parameters mean ADC 1.3 x10-3, maximum ADC 1.7 x10-3, minimum ADC .9 x10-3, kurtosis 2.9 & skewness 0.19.



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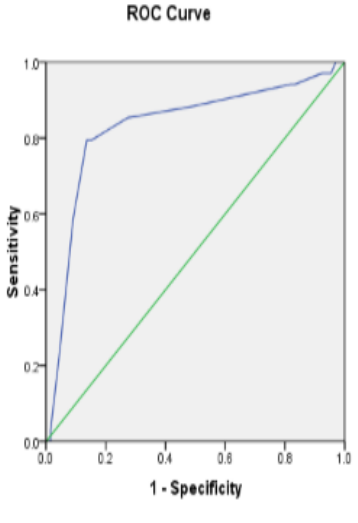

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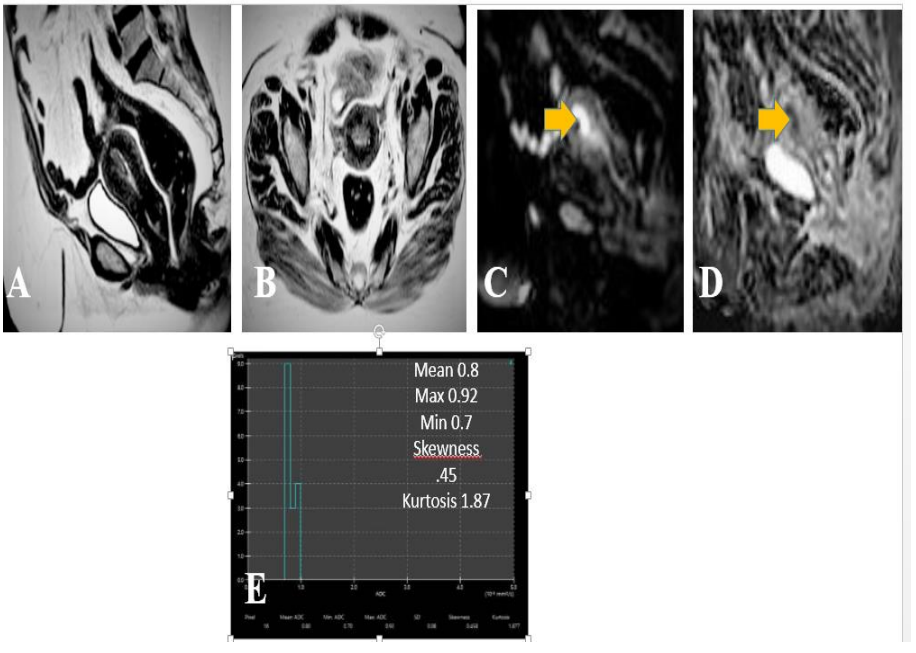
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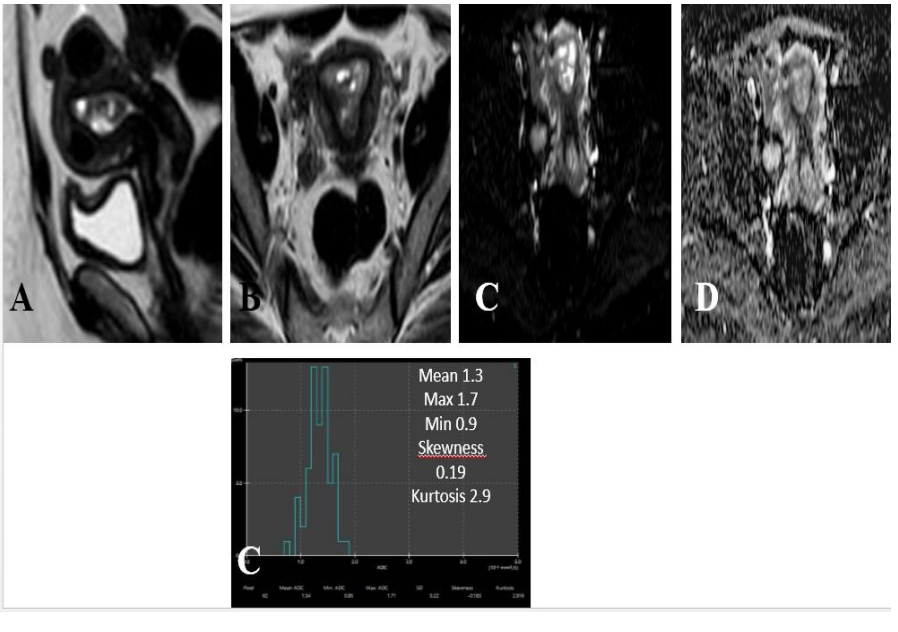
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Skewness
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