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Original article

Value of Apparent Diffusion Coefficient (ADC) Ratio To discriminate Common Benign and Malignant Hepatic Focal Lesions at MRI diffusion study.

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Abstract

Background: Diffusion-weighted imaging (DWI) is a novel imaging technique with a growing application in onco- imaging. This modality evaluates the diffusion of water molecules in various tissues, which is restricted in hypercellular regions such as malignant tissue. Apparent diffusion coefficient (ADC) is a method that can quantify the degree of restriction in tissues and can have diagnostic roles in the characterization of hepatic lesions. The ratio of ADC values between a lesion and the background liver can potentially negate these external factors and provide a more accurate representation of change in the diffusion with respect to normal tissue. **Aim:** Our study aimed to investigate the usefulness of ADC ratio of a solid liver lesion to liver parenchyma to discriminate between benign and malignant lesions. **Methods:** This was a cross sectional study conducted on all patients with hepatic solid focal lesion (benign or malignant), starting from 10-2019 to 4-2020. All patients were subjected to: Full history taking including, Radiological investigations, and Laboratory investigations. **Result:** There was significant difference between benign and malignant group as regards lesion: liver ADC ratio. **Conclusion:** Lesion to background liver ADCratio is superior in discriminating between benign and malignant focal lesions compared to

absolute ADC values of the hepatic lesions. With increasing ADCratio, there is a trend towards benignity. A cut off of ADCratio below 0.9 reflected malignancies while ADCratio above 1.5 reflected benign aetiology. These cut offs can be validated further with further studies with larger number of individual malignant and benign lesions.

1. Introduction:

Magnetic Resonance Imaging (MRI) has superior sensitivity and specificity in diagnosing focal liver lesions when compared to Computer Tomography (CT) and Ultrasound (US) [1]. Diffusion weighted imaging (DWI) is one of the non-contrast MRI sequences which are playing increasing role in the hepatic MRI interpretation [2].

Diffusion restriction within the tissue of interest demonstrated on DWI can be quantitatively measured by apparent diffusion coefficient (ADC) map [1, 3]. There has been promising evidence that ADC may be a viable tool to help discriminate benign versus malignant character of a hepatic lesion [3].

Calculation of ADC values in a particular lesion can vary with MRI equipment, scanning protocol and analysis software platform used for calculation. ADC values can also vary within the same patient in two different sets of examinations due to variation in biological parameters e.g. vascularity, membrane permeability changes [4].

In an earlier study, ADC ratio values were found to have better sensitivity and specificity than stand-alone ADC values in the interpretation of hepatic malignancies and the ratio of ADC values between a lesion and the background liver can potentially negate these external factors [4]. This study aimed to investigate the usefulness of ADC ratio of a solid liver lesion to liver parenchyma to discriminate between benign and malignant lesions.

2. Patients and Methods:

This study was a cross sectional study conducted in Radiology Department of Beni-Suef University Hospitals. Sample size was calculated by G*power version 3.1.9.2, actual power 0.802 (80.13). This study conducted upon 50 cases of liver solid lesions as following:25 cases with benign solid focal lesion and 25 cases with malignant solid focal lesion. This study included patients with hepatic solid focal lesion (benign or malignant) on cirrhotic or normal liver parenchyma.

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2.1 Inclusion criteria:

1 Patients were having single or multiple solid hepatic focal lesions (benign or malignant)

2. Age between 20 and 80 years.

3. Both sexes.

Exclusion criteria:

1. Patients having hepatic focal lesion less than 10 mm.
2. Patients receiving chemo or radiotherapy
3. Patient having simple hepatic cysts
4. Declined informed consent.

2.2 All patients were subjected to: The eligible subjects included in this study will be subjected to the following:

Informed consent was obtained from each participant. Full history including: Patient personal data: Age, sex, smoking, occupation, and residence and relevant medical history. Clinical Examination: Vital signs: temperature, pulse, blood pressure and abdominal examination. Radiological investigations: Dynamic MRI liver: All patients underwent liver MR at 1.5T (Magnetom Verio, Siemens Healthcare, Erlangen, Germany; Magnetom Trio, Siemens Healthcare), using a 32-channel phased-array coil. In addition, HBP images were obtained 10 minutes and 20 minutes after beginning contrast medium injection. Respiratory-triggered T2-weighted fast spin echo sequence, T2*-weighted GRE sequence, and DWI were obtained between DP, 10-minute, and 20-minute delayed HBP in the axial plane; 10-minute and 20-minute delayed images were also scanned in the coronal plane. The MRI radiological features of benign and malignant focal lesions were applied to discriminate between benign and malignant focal lesion. Benign features: peripheral arterial enhancement with gradual filling in portal and venous phases. Malignant features: arterial enhancement with porto venous wash out. Diffusion weighted image (DWI): DWI was obtained using a SSEPI sequence with FB. To shorten the echo train length (ETL), the parallel imaging technique (generalized autocalibrating partially parallel acquisitions; GRAPPA) with a 2-fold acceleration factor was used. A linear (least square) fit between the logarithm of the eight trace-weighted images –ln (IT(b)) and b was performed on a pixel-by-pixel basis. The slope of the result = ADC total was set equal to the corresponding pixel value of the ADC map. The ADC value was read in all focal lesions (benign and malignant) which measuring more than 1 cm, away at least 1 cm from vessels and ADC value reading away from necrotic or cystic region of the large lesions. The applied ADC ratio equation: ADC lesion : ADC liver parenchyma.

Statistical methodology:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. Kruskal-Wallis test was used to assess the statistical significance of the difference of a non-parametric variable between more than two study groups. Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups.

3. Results:

Fifty patients (25 with benign HFLs and 25 with malignant HFLs) were included in this study. Their ages ranged from 20 to 80 years with ADC map applied on all patients.

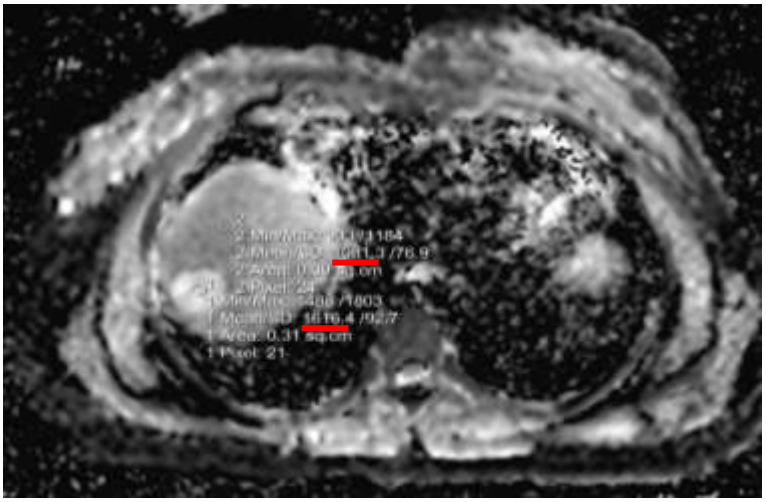

Figure (1): 43 female patient with HFL is seen at abdominal U/S. Dynamic MRI was done this figure showing ADC map of liver showing HFL and ROIs were applied on both HFL (ROI 2 reading 1616) and on liver parenchyma (ROI 1 reading 1081). ADC ratio = 1.49

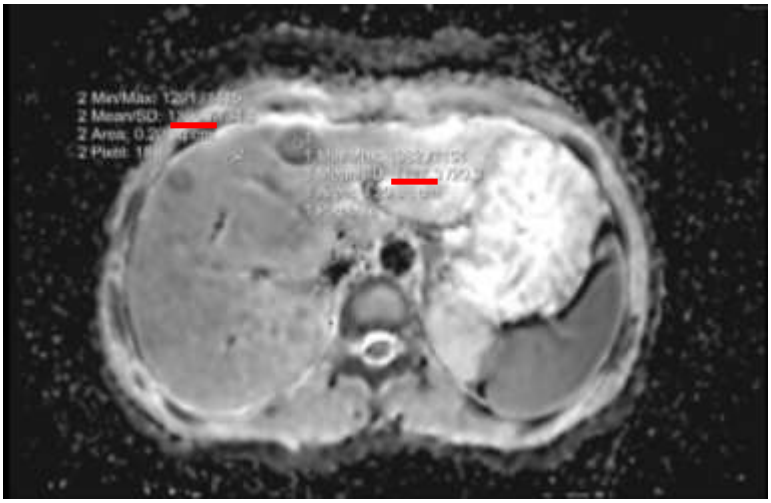

Figure (2): 38 female patient with breast cancer showing HFLs on metastatic workup. Dynamic MRI was done this figure showing ADC map of liver showing HFLs and ROIs were applied on both HFL (ROI 1 reading 1117) and on liver parenchyma (ROI 2 reading 1366). ADC ratio = 0.81

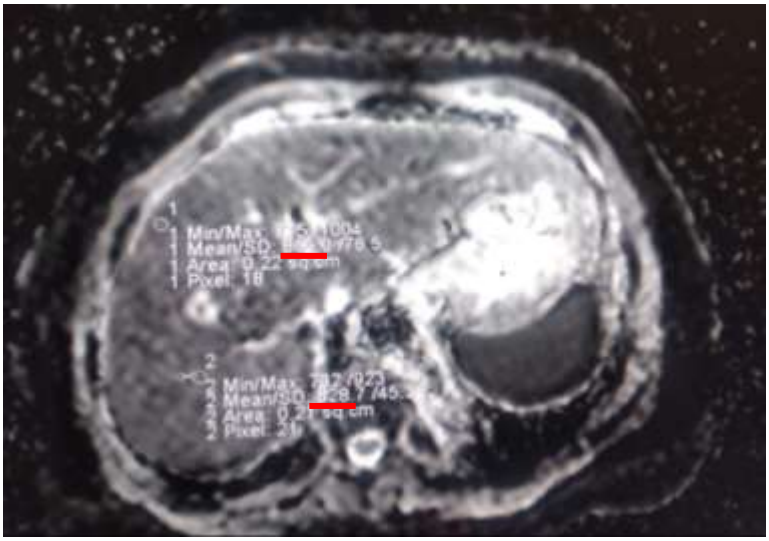

Figure (3): 65 female patient with cirrhotic liver showing HFL on routine follow up. Dynamic MRI was done this figure showing ADC map of liver showing HFL and ROIs were applied on both HFL (ROI 2 reading 828) and on liver parenchyma (ROI 1 reading 865). ADC ratio = 0.95

Table (1): Comparison between the two studied groups according to demographic data

Demographic data	Total (n = 50)		Benign (n = 25)		Malignant (n = 25)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Gender								
Male	23	46.0	13	52.0	10	40.0	$\chi 2$=	
Female	27	54.0	12	48.0	15	60.0	0.725	0.395
Age								
Min. – Max.	25.0 ±77.0		25.0 –77.0		38.0 –72.0			
Mean ± SD.	52.34 ±14.30		46.84 ±15.46		57.84 ±10.75		U=	
Median (IQR)	52.0 (42.0–65.0)		43.0 (38.0–55.0)		61.0 (48.0–67.0)		172.0	0.006*

IQR: Inter quartile range SD: Standard deviation

$\chi 2$: Chi square test U: Mann Whitney test

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

Table (1): show significant difference between benign and malignant group as regards age (46.84 ± 15.46 vs 57.84 ± 10.75, p = 0.006).

Table (2): Comparison between the two studied groups according to ADC lesion value and ratio.

ADC	Total (n = 50)	Benign (n = 25)	Malignant (n = 25)	Test of Sig.	p
Lesion Min. – Max. Mean ± SD. Median (IQR)	 124.0 –2892.0 1395.16 ±597.91 1281.5(896 – 1791)	 1201.0 –2892.0 1829.88 ±449.06 1757(1499 – 2123)	 124.0 –1872.0 960.44 ±366.76 896 (815 –1018)	 t= 7.498*	 <0.001*
Ratio Min. – Max. Mean ± SD. Median (IQR)	 0.13 –3.04 1.24 ±0.61 1.24 (0.75 –1.50)	 1.04 –3.04 1.68 ±0.51 1.50 (1.35 –1.90)	 0.13 –1.44 0.79 ±0.29 0.75 (0.64 –0.89)	 U= 17.0	 <0.001*

IQR: Inter quartile range SD: Standard deviation

U: Mann Whitney test t: Student t-test

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

Table (2): show significant difference between benign and malignant group as regards ADC lesion and ADC ratio.

Table (3): Diagnostic performance for ADC lesion to discriminate malignant (n=25) from benign (n=25)

	AUC	p	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
ADC lesion	0.938*	<0.001*	0.869 – 1.006	≤1191	84.0	100.0	100.0	86.2

AUC: Area Under a Curve p value: Probability value

CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$ #Cut off was choose according to Youden index

Table (3): The calculated area under the ROC curve for to discriminate malignant from benign was 0.938 (95 % CI 0.869, 1.006), with a sensitivity of 84 % and a specificity of 100%, using a cut-off ADC lesion value of 1191.

Table (4): Comparison between the two studied groups according to cirrhotic and diagnosis

	Total (n = 50)		Benign (n = 25)		Malignant (n = 25)		χ2	p
	No.	%	No.	%	No.	%		
Cirrhotic/Not								
No	33	66.0	22	88.0	11	44.0	10.784	0.001*
Yes	17	34.0	3	12.0	14	56.0		
Diagnosis								
HCC	15	30.0	0	0.0	15	60.0	21.429*	<0.001*
Regenerative	3	6.0	3	12.0	0	0.0	3.191	FEp=0.235
Mets	10	20.0	0	0.0	10	40.0	12.500*	<0.001*
Hemangioma	22	44.0	22	88.0	0	0.0	39.286*	<0.001*

χ2: Chi square test FE: Fisher Exact

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

Table (4): show significant difference between benign and malignant group as regards cirrhosis and Diagnosis.

Table (5): Diagnostic performance for ADC lesion to discriminate malignant (n=14) from benign (n=3) in Cirrhotic group

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
ADC lesion	0.881	0.044*	0.716 – 1.000	≤1260	85.71	66.67	92.3	50.0

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

Table (5): The calculated area under the ROC curve for to discriminate malignant from benign was 0.881 (95 % CI 0.716, 1.000), with a sensitivity of 85.71 % and a specificity of 66.67%, using a cut-off ADC lesion value in cirrhotic < 1260.

Table (6): Diagnostic performance for ADC ratio to discriminate malignant (n=14) from benign (n=3) in Cirrhotic group

	AUC	p	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
ADC ratio	0.929	0.023*	0.800 – 1.000	≤0.986	85.71	100.0	100.0	60.0

AUC: Area Under a Curve p value: Probability value

CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

#Cut off was choose according to Youden index

Table (6): The calculated area under the ROC curve for to discriminate malignant from benign was 0.929 (95 % CI 0.800, 1.000), with a sensitivity of 85.71 % and a specificity of 100 %, using a cut-off ADC ratio in cirrhotic < 0.986.

Table (7): Diagnostic performance for ADC lesion to discriminate malignant (n=11) from benign (n=22) in Non-Cirrhotic group

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
ADC lesion	0.946	<0.001*	0.856 – 1.000	≤1201	81.82	95.45	90.0	91.3

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

Table (7): The calculated area under the ROC curve for to discriminate malignant from benign was 0.946 (95 % CI 0.856, 1.000), with a sensitivity of 81.82 % and a specificity of 95.45 %, using a cut-off ADC lesion value in non-cirrhotic < 1201.

Table (8): Diagnostic performance for ADC ratio to discriminate malignant (n=11) from benign (n=22) in Non-Cirrhotic group

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
ADC ratio	0.971	<0.001*	0.912 – 1.000	≤1.156	90.91	95.45	90.9	95.5

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

Table (8): The calculated area under the ROC curve for to discriminate malignant from benign was 0.971 (95 % CI 0.912, 1.000), with a sensitivity of 90.91 % and a specificity of 95.45 %, using a cut-off ADC ratio in non-cirrhotic < 1.156.

4. Discussion

Differentiation between malignant and benign FLLs and establishing the correct diagnosis are of great importance in treatment planning for patients with liver neoplasms and in patients without neoplasms for avoiding unnecessary liver biopsies. [5] (Figure 1&2)

The aim of this project is to investigate the usefulness of ADCratio of a solid liver lesion to liver parenchyma to discriminate between benign and malignant lesions.

In this study we found that there was significant difference between benign and malignant group as regards age (46.84 ± 15.46 vs 57.84 ± 10.75, p = 0.006).

Alnaghy et al. 2018 [6] and Xia et al. 2015 [7] found that is a significant age difference between the malignant and benign groups (t=3.905, p=0.0001).

In this study we demonstrated that there was significant difference between benign and malignant group as regards AFP (0.89 ± 0.26 vs 1.24 ± 0.22 and 2.31 ± 2.05 vs 207.38 ± 256.60, p <0.001).

Jiang et al. 2022 [8] and Bröker et al. 2014 [9] found that the AFP level of malignant lesions was higher than that of benign lesions.

In this thesis we illustrated that there was significant difference between benign and malignant group as regards ADC lesion and ADC ratio.

Abdurrahman et al. 2020 [10], Yilmaz et al. 2018 [11], Cieszanowski et al. 2012 [12], Koike et al. 2009 [13], Karim et al. 2021 [14], Hasan et al. 2016 [17]. found that there was a statistically significant difference in ADC value between the benign and malignant lesions (p<0.001).

Jain et al. 2018 [2] found that Mean ADCratio for benign lesions : background liver parenchyma was 1.3467 and for malignant lesions was 0.9038. There was a statistically significant difference between these values

($p < 0.001$). All lesions with ADCratio less than 0.9 were malignant while all lesions with ADCratio greater than 1.5 were benign

Also, Jain et al. 2018 [2] defined an ADC value of 1.26 x 10-3 mm2 /s to be the best available cutoff value for differentiating benign and malignant lesions, achieving sensitivity and specificity of 92% and 80%, respectively.

Within the same context, Hasan et al. 2016 [16] reported that by using ADC cut-off of 1.6 x 10 -3 mm2 /s led to the highest accuracy for the differentiation of malignant and benign liver lesions (86%) with a sensitivity of 100% and specificity of 68% for malignant lesions. Its strength was in its 100% NPV where ADC values above 1.6 x 10-3 mm2 /s exclude the malignant lesions.

Our study concluded that lesion to background liver ADCratio is superior in discriminating between benign and malignant focal lesions compared to absolute ADC values of the hepatic lesions. With increasing ADCratio, there is a trend towards benignity. A cut off of ADCratio below 0.9 reflected malignancy while ADCratio above 1.5 reflected benign aetiology regardless the status of parenchyma. In spite of, the difference of cut off in ADC value in discriminating malignancy and benign aetiology regard the liver parenchyma status. As the following: A cut off ADC value of the lesion below 1260 reflected malignancy while ADC value of the lesion above 1518 reflected benign aetiology in cirrhotic liver parenchyma. And a cut off ADC value of the lesion below 1201 reflected malignancy while ADC value of the lesion above 1297 reflected benign aetiology in normal liver parenchyma.

These ADCratio cut offs can be validated further with further studies with larger number of individual malignant and benign lesions.

5. Conclusion and Recommendations:

Our study concluded that lesion to background liver ADCratio is superior in discriminating between benign and malignant focal lesions compared to absolute ADC values of the hepatic lesions. With increasing ADCratio, there is a trend towards benignity. A cut off of ADCratio below 0.9 reflected malignancies while ADCratio above 1.5 reflected benign aetiology. These cut offs can be validated further with further studies with larger number of individual malignant and benign lesions.

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