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Original Article

Value of diffusion-weighted MRI in evaluation of solid hepatic focal lesions in patients with renal insufficiency

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ABSTRACT

Objectives: To evaluate the diagnostic accuracy of diffusion weighted MRI in diagnosis of solid hepatic focal lesions in patients with impaired renal functions.
Patients and methods: This prospective study included (30) patients with impaired renal function and had solid hepatic focal lesions based on ultrasound examination. All patients subjected to diffusion MRI examination and ADC measurement, and the data obtained were compared with histopathological results of malignant lesions and previously reported appearance of benign lesions.
Results: There were 57 solid focal lesions in the included 30 patients. The mean ADC value of hemangiomas was 2.03×10^{-3}, lipoma was 0.1×10^{-3}, HCC was 1.06×10^{-3} and for metastases was 1.2×10^{-3}. Benign lesions have significant higher ADC values than malignant ones ($p = 0.003$), and in malignant lesions the primary hepatic carcinomas had lower ADC values compared to metastatic lesions which had no significant value. Using a cutoff value of 1.6×10^{-3} for the ADC to differentiate between benign and malignant lesions the AUC was 90% with Sensitivity, Specificity, PPV, NPV and accuracy of 92%, 80%, 98%, 50% and 91% respectively.
Conclusion: DW-MRI and ADC value measurements are effective in characterizing solid focal hepatic lesions without contrast injection in patients with renal impairment.

1. Introduction

Management planning and treatment options of different focal liver pathologies require an accurate detection and characterization of these focal masses [1,2]. Imaging of focal liver lesions by different imaging tools including ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) is crucial, not only in the diagnosis but also in the follow-up [3]. Precise localization, measurement and numbering of focal liver lesions (FLLs) are important to decide how to manage and how to follow [1,2].

Due to its high tissue contrast resolution, lack of ionizing radiation and the capability of performing different functional imaging sequences, and MR imaging of different liver pathologies with and without IV contrast administration is of increasingly important role in evaluation of such patients [4].

However, one of the most important limitations for giving IV contrast is renal complications [5]. Patients with reduced renal function are at risk of developing contrast-

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induced nephrotoxicity (CIN) following a contrast-enhanced computed tomography examination with an iodinated contrast agent [1] and at risk of developing nephrogenic systemic fibrosis (NSF) after a contrast-enhanced MRI examination with an extracellular gadolinium-based contrast agent [5,6].

Patients with estimated glomerular filtration rate (eGFR) < 30 mL/min, including those on dialysis or waiting for liver transplantation, should not receive nonionic linear chelates. The lowest possible dose of stable Gd contrast agents (macrocyclic chelates) should be used in these patients [7]. Contrast-enhanced MRI examination should be avoided whenever possible during pro-inflammatory events, although hemodialysis shortly after Gd contrast administration has not been shown to prevent NSF [8].

Consideration should be given to imaging techniques that may offer the same diagnostic information without needing to administer contrast materials [5,6].

With recent advances in technology, DW-MRI is reaching a potential for clinical use in the abdomen, particularly in the liver. DW MR imaging is an attractive technique for multiple reasons: it can potentially add useful qualitative and quantitative information to conventional imaging sequences; it is quick (performed within a breath hold), can be easily incorporated and is a non-enhanced technique (performed without the use of gadolinium-based contrast media), thus easy to repeat, and useful in patients with severe renal dysfunction at risk for developing nephrogenic systemic fibrosis [9–11].

The aim of this study was to evaluate the diagnostic accuracy of diffusion weighted MRI in diagnosis of solid focal liver lesions in patients with impaired renal function.

2. Patients and methods

This prospective study was carried out during the period from September 2014 to November 2015 and included thirty patients with impaired renal function and had solid focal liver lesions referred to Radiodiagnosis Department from General Medicine, Oncology and Tropical Departments of Zagazig University Hospitals. They were 16 males and 14 females, and their ages ranged from 28 to 70 years.

The study was approved by our institutional ethics committees and a written consent was obtained from each patient before participating in the study.

2.1. Study design

During the study period thirty patients with impaired renal function (eGFR < 30) and diagnosed to have solid focal liver lesions based on ultrasound examination were included in the study. Exclusion criteria were previous intervention to the focal lesion as biopsy or chemoembolization, patients unfit for or having contraindication to MRI examination. The included patients were subjected to full clinical and laboratory evaluation, followed by MRI examination.

Our study encountered 57 solid focal masses (15 patients had multiple lesions, one case of hemangioma, 4 cases of HCC and 10 cases of metastasis).

Final diagnosis was based on histopathological examination in 26 patients. The remaining 4 cases (3 cases of hemangioma and one case of lipoma) did not need biopsy as they were diagnosed by their characteristic MRI findings previously described in the literature [12,13].

2.2. Protocol for liver MRI

Abdominal MR examination was performed using 1.5 tesla superconducting MR scanner (Intera Achiva Nova Dual system, Philips Medical System, Best, the Netherlands) with abdominal coil in supine position as follows:

a. Conventional MRI was performed using the following:
   - Gradient echo T1 weighted images (WI) were performed with the following parameters: (TR = 4–5 ms, TE = 2 ms, 375 × 375 field of view (FOV), 256 × 256 matrix, Flip angle(FA) = 10°, section thickness 5–7 mm), T1 in-phase and out-of-phase (TR/TE, 110/5 ms; in-phase; out-of-phase TR/TE, 110/2 ms; FA = 70; matrix, 256 × 256; slice thickness, 5–7 mm; FOV, 375 × 375).
   - T2-weighted images (TR = 418 ms, TE = 80, Flip angle = 90°, 375 × 375 FOV, 256 × 256 matrix and section thickness: 5–7 mm).
   - Heavily T2WI (TR = 1095 ms, TE = 200, Flip angle = 90°, 375 × 375 FOV, 256 × 256 matrix and section thickness: 5–7 mm).
   - Axial STIR (Short time inversion recovery): (TR = 418 ms, TE = 80, TI = 140 ms, FA = 90°, 375 × 375 FOV, 256 × 256 matrix and section thickness 5–7 mm).

b. Diffusion weighted MR imaging (DW-MRI):

DW-MRI was obtained with a single-shot spin-echoplanar sequence (TR/TE, 2800-3600/74, FA 90°, matrix: 128 × 128, section thickness 5–8 mm, intersection gap 1 mm and FOV 380 × 380).

Two different b values ($b = 0$ and 1000 mm^2/s) and three directions were used.

2.3. Image interpretation

All MRI images were transferred to workstation and reviewed by a radiologist unaware about the clinical data and ultrasonographic findings of the patients. The ADC value of the described liver lesions was measured by placing the circular region of interest (ROI) as follows: the largest diameter of lesions was measured first; in large lesions >1 cm three regions of interest (ROIs) were marked off and measured in the same image and a mean value of SI was acquired for ADC calculation; in smaller lesion ⩽1 cm one ROI was measured in its center; and for patients with multiple lesions the ADC values of at least two lesions were measured and an average ADC was included in the result. In all lesions the regions of blood vessels, necrosis and artifacts were excluded during measurement.

2.4. Histopathological examination

Histopathological examination was performed in 26 patients using fine needle aspiration in 23 patients (12 patients of HCC and 11 patients of metastases), and true cut biopsy in 3 patients (2 patients of HCC and 1 patient of metastases) both done using ultrasound guidance.

The primary site for metastatic lesions was breast cancer ($n = 6$), colorectal carcinoma ($n = 4$), renal cell carcinoma ($n = 1$) and bronchial carcinoma ($n = 1$).

2.5. Statistical analysis

ADC value of each lesion was compared with ADC of normal hepatic parenchyma using Mann–Whitney and paired *t*-tests. Data were expressed as mean (SD) unless otherwise indicated and one way analysis of variance (ANOVA) was used to compare the mean values between the studied groups. For significant finding a post-ANOVA pairwise comparison of mean was concluded and p value <0.05 was considered significant. Also we use receiver operating curve (ROC) to characterize benign and malignant lesions. Validity of ADC for diagnosis of focal liver lesions was tested by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and measure of agreement (Kappa test).

3. Results

We included 30 patients with 57 solid focal liver lesions, they were 16 males (63%) and 14 females (47%) and their age ranged from 28 to 70 years with mean age 51.6 ± 11.5 years.

The final diagnosis of the 57 included masses was as follows: 52 (91%) malignant hepatic masses (18 HCC (32%) and 34 (59%) metastasis), and 5 (9%) benign masses (4 (7%) hemangioma and one (2%) lipoma). Thirty-seven (64%) of the 57 focal liver lesions were located in the right lobe and 20 (36%) were in the left lobe. The diameter of the lesions ranged between 5 and 157 mm with the mean size of 21.6 ± 4 mm.

The mean ADC value for HCC was 1.06 ± 0.30 (range: 0.59×10^{-3} mm^2/s and 1.5×10^{-3} mm^2/s) (Fig. 1); for metastasis the mean ADC value was 1.2 ± 0.57 (range: 0.5×10^{-3} mm^2/s and 2.21×10^{-3} mm^2/s) (Figs. 2 and 3); for hemangiomas it was 2.03 ± 0.41 (range: 1.7×10^{-3} mm^2/s and 2.5×10^{-3} mm^2/s) (Fig. 4), (Table 1); and the measured ADC value in the case of lipoma was 0.1×10^{-3} mm^2/s (Fig. 5) (see Table 2).

There was an overlap in the ADC value between hemangioma and metastasis but the mean ADC value of metastasis was significantly lower ($p = 0.05$); on the other hand although an overlap was existed in the mean ADC value between HCC and metastasis, the HCC was found to had lower values; however, the difference was not significant ($p = 0.33$).

Validity of ADC value for distinguishing benign and malignant solid masses was evaluated using receiver operating curve (ROC), and we found that at ADC value of 1.6×10^{-3} mm^2/s as a cutoff value the reported sensitivity was 92%, a specificity of 80%, PPV of 98%, NPV of 50% and accuracy of 91% (Table 3) (Fig. 6).

4. Discussion

Planning strategy for Management of patients suffering from solid focal liver lesions depends upon correct characterization of these lesions as benign or malignant. Importance of the role of magnetic resonance imaging in the evaluation of different liver pathologies is always increasing owing to its high contrast resolution, and the possibility of performing functional imaging sequences [4].

Recently, intravenous gadolinium based contrast is claimed to be responsible for developing NSF in patients with renal insufficiency; hence, the need to develop novel MRI techniques that do not require gadolinium becomes insisting. DW-MRI is non-invasive, rapidly acquired, and does not require administration of intravenous gadolinium. This technique utilizes the measurement of thermally induced random molecular motion in biological tissues, known as Brownian motion [14].

The aim of this study was to evaluate the diagnostic efficiency of DW-MRI in differentiating benign and malignant solid focal liver lesions in patients with impaired renal functions.

We included 30 patients with 57 solid hepatic focal lesions. DW-MRI was performed for all patients with the measurement of the ADC value of the masses, and the results were compared and correlated with those of histopathological results.

Appearances of focal liver lesions on DWI especially at high b values were reported to be diagnostic in several studies due to restricted diffusion and increased signal intensity on DW images [15]. However, Abdel Latif et al. [16] in their study stated that this measurement was a qualitative assessment and represented a subjective interpretation.

Also, the results of Parikh et al. [17] show improved detection of malignant and benign FLLs by using DW imaging compared with standard breath-hold T2-weighted imaging, with equivalent performance of DW imaging and T2-weighted imaging for lesion characterization.

In our study in accordance with the Abdel Latif et al. [16] and Parikh et al. [17] benign and malignant solid hepatic masses show nearly the same pattern of appearance with restricted diffusion and difficulty to discriminate the nature of the lesion; as in hemangiomas appeared as well defined hyperintense lesions, and on ADC map they appeared isointense in three lesions (75%) and as hyperintense with central hypointense area, and on ADC map appeared as isointense with central area of hypointensity in one lesion (25%). On the other hand twelve lesions (66%) of HCC appeared as multiple hyperintense, and four lesions (22%) appeared as mixed intensity of hyperintense and isointense signal, and another two lesions (11%) appeared as mixed intensity of hyperintense and hypointense signal, whereas on the ADC maps all the lesions were of hypointense signal.

Metastatic lesions appeared as multiple hyperintense in thirty-two (94%) lesions; two lesions (6%) displayed mixed

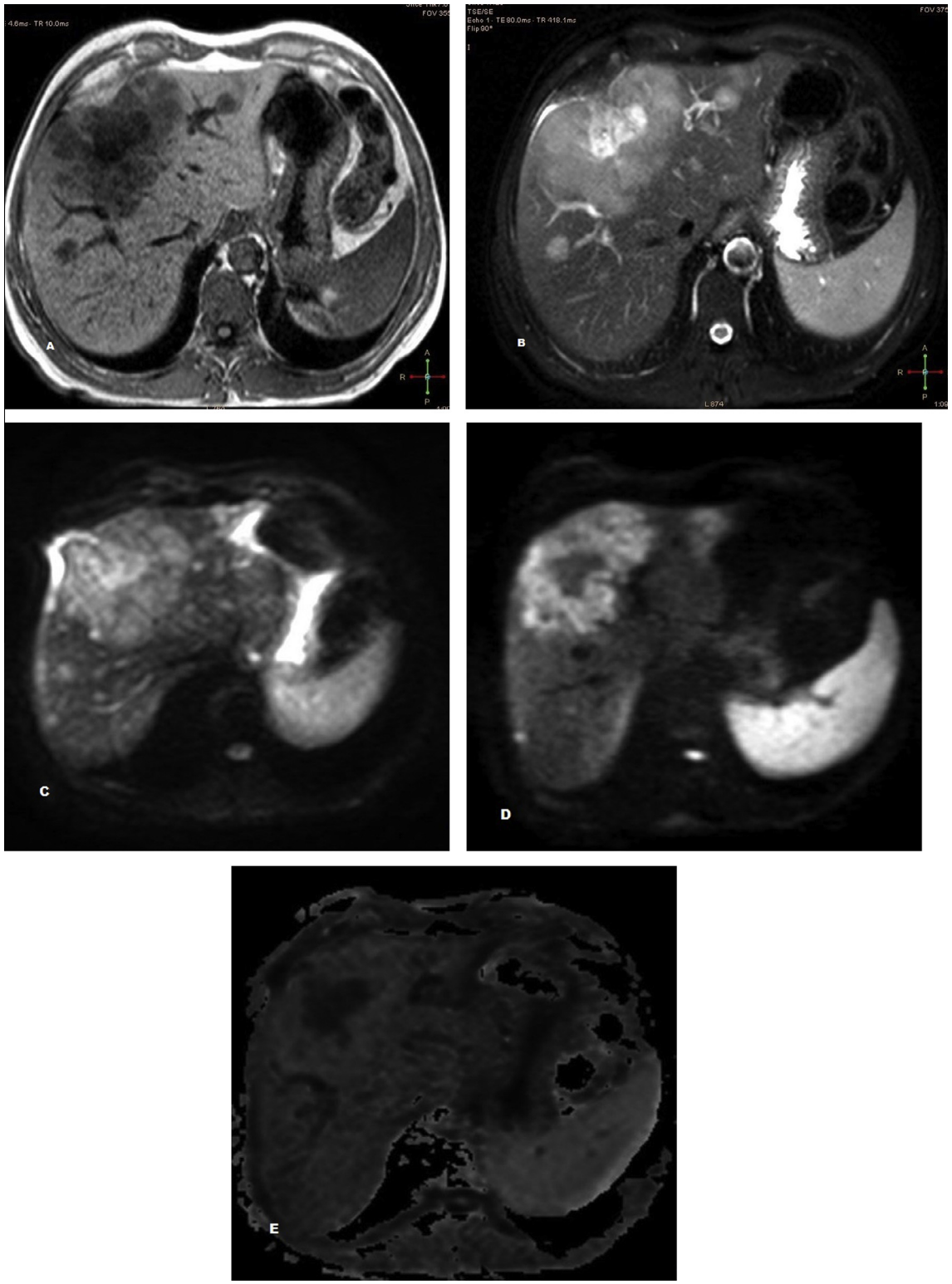

Fig. 1. MR imaging of multi-centric HCC in a 45 years old patient. (A) Axial T1GE reveals large hypointense focal lesion with central area of marked hypointensity affecting mainly segment VIII, with multiple hypointense satellites around it scattered all over the liver. (B) Axial T2 reveals large hyperintense focal lesion with central area of marked hyperintensity with multiple hyperintense satellites around it. (C) Diffusion weighted echoplanar image with (b = 0) shows that the lesion displays mixed hyperintense signal. (D) Diffusion weighted echoplanar image with (b = 1000) shows that the lesion remains hyperintense with central area of hypointensity. (E) ADC map of the lesion reveals hypointensity. The lesion has ADC value of 1.52×10^{-3} mm^2/s suggestive of malignant lesion.

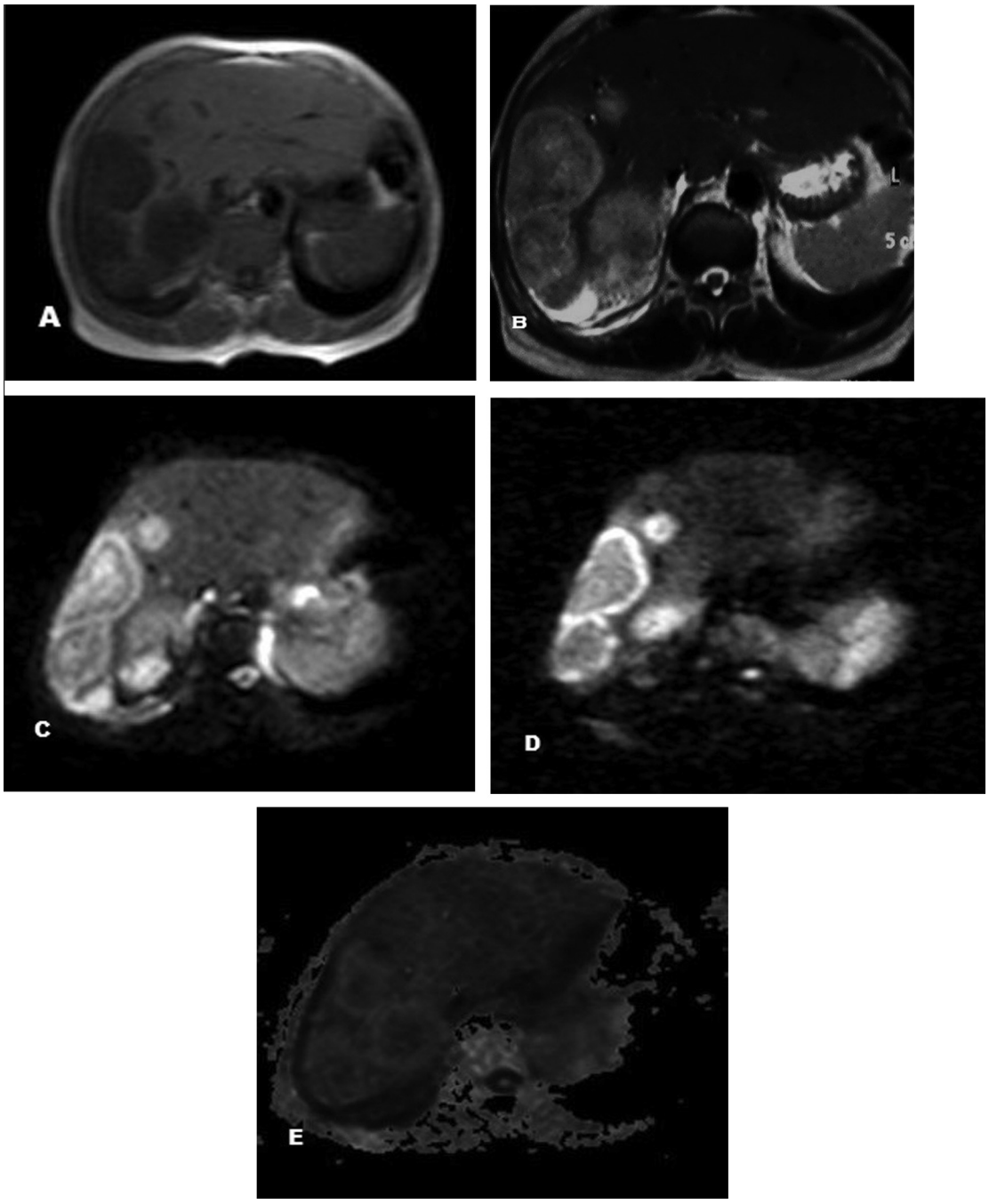

Fig. 2. MR imaging of metastatic renal cell carcinoma in a 60 years old patient. (A) Axial T1GE reveals multiple hypointense focal lesions in the Rt lobe of the liver. (B) Axial T2 reveals multiple lesions of heterogenous hyperintensity. (C) Diffusion weighted echoplanar image with (b = 0) shows that the lesions show mixed intensity of isointensity and hyperintensity mainly hyperintensity. (D) Diffusion weighted echoplanar image with b = 1000 shows that the lesions show mixed hyperintensity. (E) ADC map of the lesion reveals hypointense signal. The lesion has low ADC value of 1.36×10^{-3} mm^2/s suggestive of malignant lesion.

intensity areas of hypo and hyper-intensity signal and at ADC maps all the lesions displayed hypointense signal.

ADC value was a measurable parameter of MRI diffusion. There were various published studies confirming the diagnostic usefulness of measuring ADC in the differentiation of focal hepatic lesions. According to these studies malignant lesions had lower ADC values than benign lesions which had been attributed to the higher cellularity of malignant lesions [17,18].

In our study in accordance with previous studies we found that there was a statistically significant difference between the mean ADC value of the benign and malignant

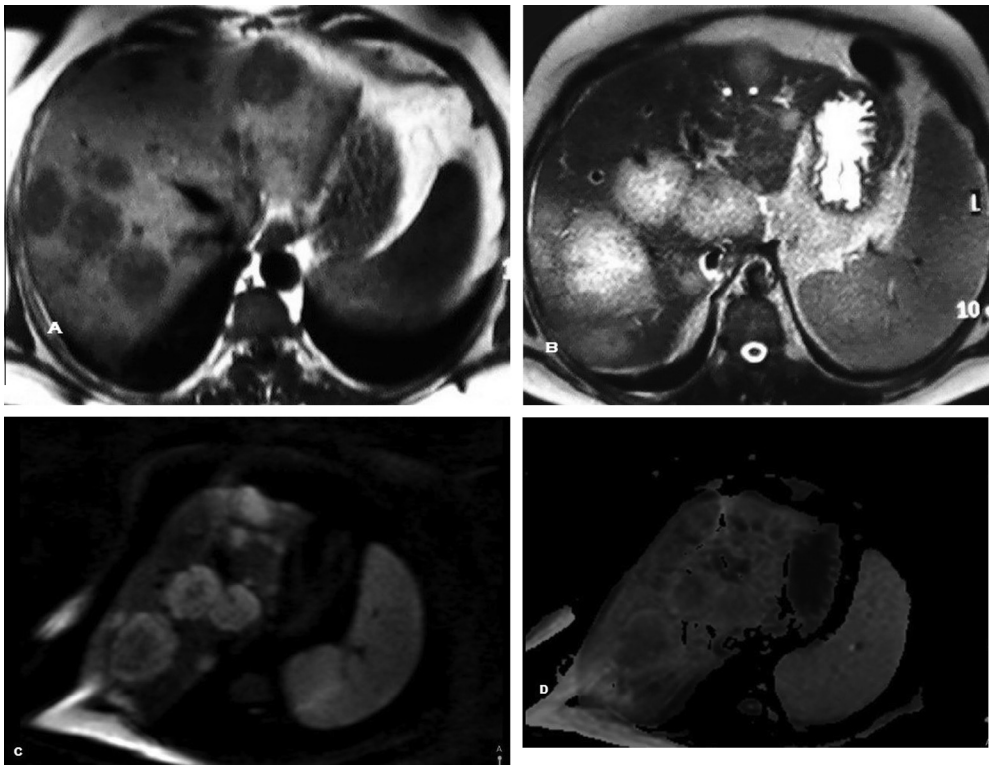

Fig. 3. MR Imaging of metastatic cancer colon in a 60 years old patient. (A) Axial T1GE reveals multiple heterogenous hypointense focal lesions affecting the whole liver. (B) Axial T2 reveals multiple hyperintense focal lesions with central areas of marked hyperintensity. (C) Diffusion weighted echoplanar image with $b = 1000$ shows mixed intensity lesions of hypointensity and hyperintensity mainly hyperintensity. (D) ADC map of the lesion reveals hypointensity. The lesion has high ADC value 2.1×10^{-3} mm^2/s.

solid hepatic focal lesion ($p = 0.003$) which was higher for the benign than malignant lesions measuring $2 \pm 0.56 \times 10^{-3}$ mm^2 and $1.13 \pm 0.45 \times 10^{-3}$ mm^2 respectively.

However Sandrasegaran et al. [19] and Miller et al. [20] in their studies declared that the ADC values of solid benign and malignant lesions were similar and DWI was not valuable in distinguishing between benign and malignant solid lesions.

The difference between mentioned studies may be due to the use of variable *b* value as diffusion gradients in studies of Sandrasegaran et al. [19] and Miller et al. [20] and they used small *b* values of 0 and 50.

In a study done by Sun et al. [21], they had evaluated the characteristics of MR imaging of hepatic focal lesions using ADC value and concluded that applying quantitative analysis of liver lesions by measuring the ADC values increases the accuracy in diagnosing these lesions.

In the study performed by Namimoto et al. [22], the ADC values of hemangiomas were smaller than those of cysts, owing to the high viscosity of the blood contents of hemangiomas which also contain numerous interstitial spaces, scars and hemorrhages restricting motion of molecules.

Ichikawa et al. [23], in their study to differentiate between the ADC value of hemangiomas, metastatic focal lesions and hepatocellular carcinomas found that the hepatic hemangiomas had shown higher ADC values than those of hepatocellular carcinomas and metastases.

Different ADC values were reported for hemangioma in the previous studies with measured value of 1.9×10^{-3} mm^2/s in study of Gourtsoyianni et al. [24] and the mean was $2.22 \times 10^{-3} \pm 0.45$ and $1.72 \times 10^{-3} \pm 0.30$ in studies of Kandpal et al. [25] and Oner et al. [26] respectively.

In this study the mean ADC value of hemangiomas was in the same range as in previous studies measuring $2.03 \times 10^{-3} \pm 0.4$ and ranged between 1.7×10^{-3} mm^2/s and 2.5×10^{-3} mm^2/s.

Also different ADC values were described for HCC and metastasis in previous reports; in the study of Gourtsoyianni et al. [24], the ADC value of HCC was 1.38×10^{-3} mm^2/s and ADC value reported by Sun et al. [27] was 0.91×10^{-3} mm^2/s, while mean ADC value reported by Kandpal et al. [25] was $1.22 \times 10^{-3} \pm 0.34$.

In accordance with these reports in our study the mean ADC of HCC was $1.06 \times 10^{-3} \pm 0.30$, ranged between 0.59×10^{-3} mm^2/s and 1.5×10^{-3} mm^2/s.

For ADC value of metastasis also different figures were encountered in the literature; in the study of Gourtsoyianni et al. [24], mean ADC value of metastases was $0.99 \times 10^{-3} \pm 0.22$, while that reported by Kandpal et al. [25] was $1.06 \times 10^{-3} \pm 0.36$; however, ADC value reported by Sun et al. [27] was 1.13×10^{-3} mm^2/s.

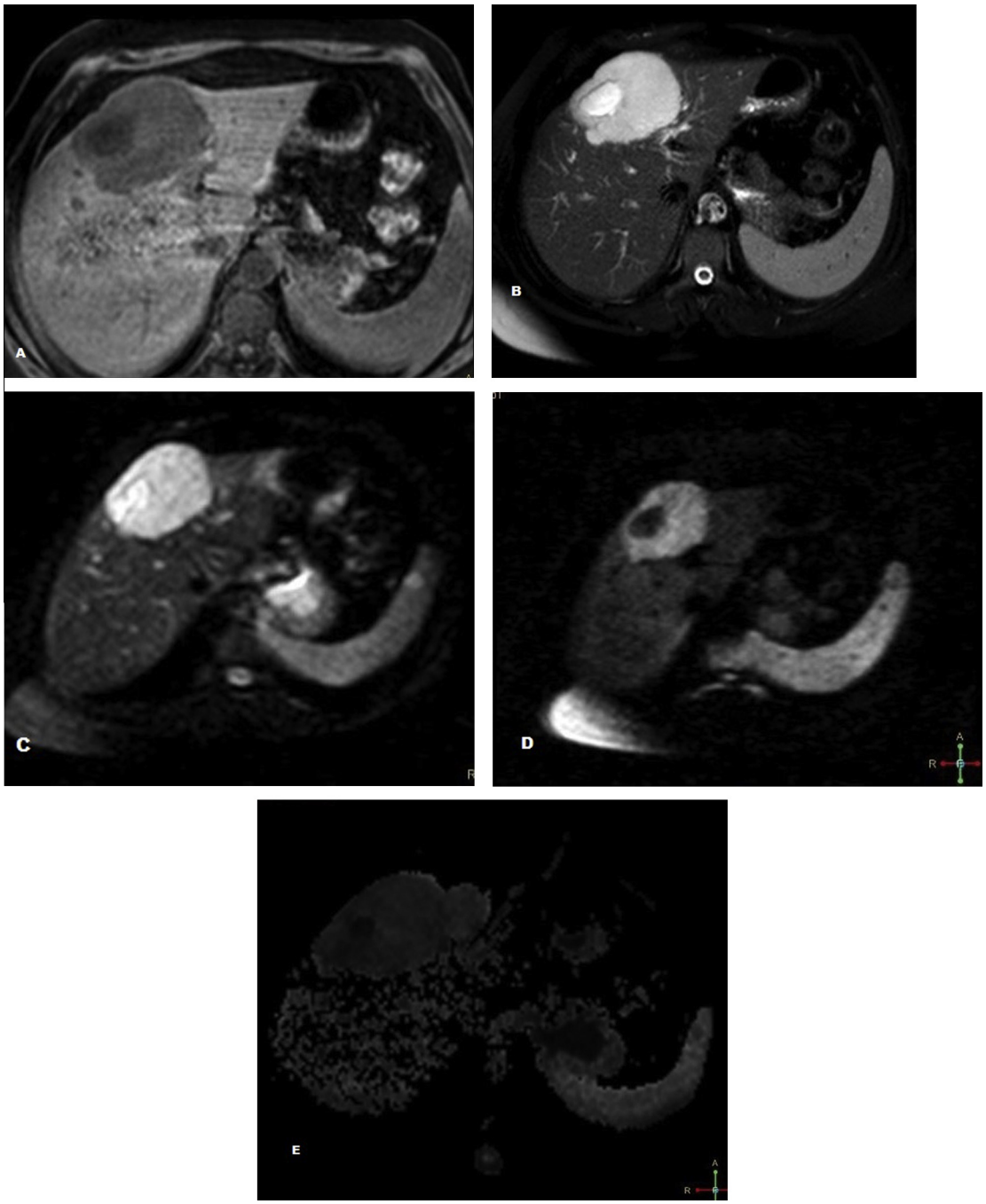

Fig. 4. MR imaging of hemangioma in a 41 years old patient. (A) Axial T1GE shows well defined hypointense lesion with central area of marked hypointensity in segments IV and VIII. (B) Axial T2WI reveals hyperintensity of the lesion with area of marked hyperintensity. (C) Diffusion weighted echo planar image with $b = 0$ shows marked homogenous hyperintense lesion. (D) Diffusion weighted echo planar image with $b = 1000$ shows hyperintense signal with central hypointense area. (E) ADC map of the lesion reveals isointense lesion with central area of hypointensity. The lesion has high ADC value of 1.9×10^{-3} mm^2/s suggestive of benign lesion.

These figures were matched with figures of this study where the mean ADC at the metastatic lesions was $1.2 \times 10^{-3} \pm 0.57$ and ranged between 0.5×10^{-3} mm^2/s and 2.17×10^{-3} mm^2/s.

Comparing the ADC value between solid malignant lesions we found that the ADC value of HCC somewhat was less than that of metastatic lesions, and this was in coincidence with Namimoto et al. [22].

From previous results we had emphasized that the presence of different ADC values for different lesions was attributed to the size of the lesion, localization of the ROI within the lesions, presence of areas of necrosis or hemor-

Table 1
Mean and range of ADC values of included liver lesions.

Pathology (57 masses)	ADC value	
	Mean	Range
Hemangioma	$2.03 \pm 0.41 \times 10^{-3}$ mm^2/s	1.7×10^{-3}–2.5×10^{-3} mm^2/s
HCC	$1.06 \pm 0.30 \times 10^{-3}$ mm^2/s	0.59×10^{-3}–1.5×10^{-3} mm^2/s
Metastases	$1.2 \pm 0.57 \times 10^{-3}$ mm^2/s	0.5×10^{-3}–2.21×10^{-3} mm^2/s

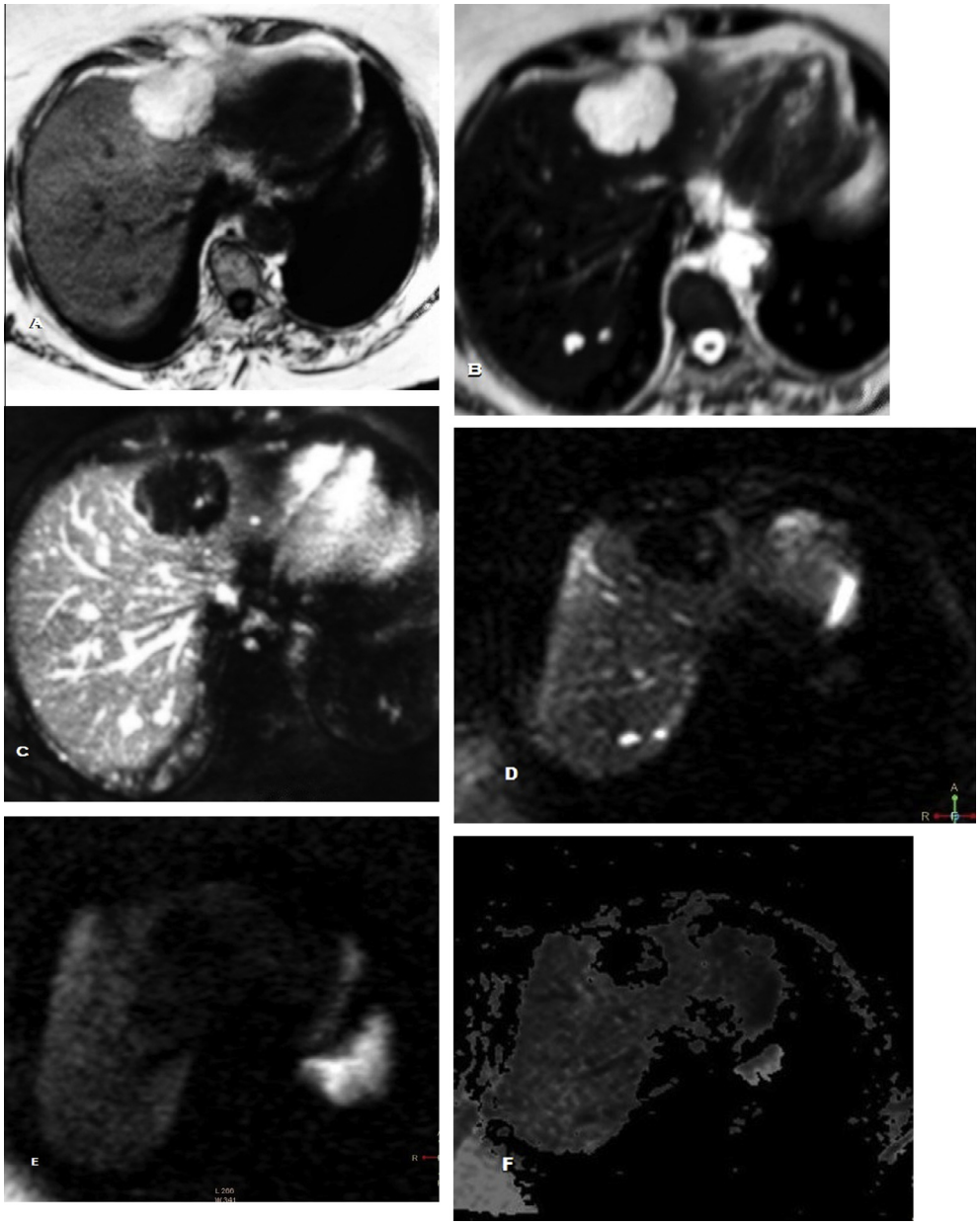

Fig. 5. MR imaging of lipoma in a 62 years old patient. (A) Axial T1GE reveals well defined hyperintense focal lesion in segment IV of Lt lobe. (B) Axial T2 reveals well defined less hyperintense lesion in segment IV of Lt lobe and another two small lesions in segment VII of the Rt lobe. (C) Axial STIR reveals hypointense focal lesion. (D) Diffusion weighted echo planar image with $b = 0$ shows that the lesion shows signal void. (E) Diffusion weighted echo planar image with $b = 1000$ shows that the lesion maintains signal void. (F) ADC map of the lesion reveals signal void. ADC value of the lesion is low 0.1×10^{-3} mm^2/s.

Table 2
Overall mean ADC value of benign and malignant masses.

		Benign (n = 4)	Malignant (n = 26)	MW	p
At lesion	ADC: (10^{-3} mm^2/s)				
	Mean ± SD	2.1 ± 1.1	1.13 ± 0.45	3.67	0.004**
	Range	0.1–2.5	0.5–2.21		

** Highly significant.

Table 3
Validity of ADC in differentiating malignant and benign focal hepatic lesions.

Cutoff	AUC	Sens.	Spec.	PPV	NPV	Accuracy	p-value
⩽1.6	0.90	92	80	98	50	91	<0.001**

** Highly significant.

rhage and the use of different b-values; however, in spite of these variations the overall ADC value for solid benign masses was higher than that of solid malignant masses and was statistically significant in our study (p = 0003).

In this study there was overlap between ADC value of hemangiomas ranged between 1.7×10^{-3} mm^2/s and 2.5×10^{-3} mm^2/s and metastases having ADC value ranged between 0.5×10^{-3} mm^2/s and 2.17×10^{-3} mm^2/s and such overlap may be due to necrosis and hemorrhage in some cases of metastatic lesions.

Also Bruegel et al. [28], in their study found that the ADC values of metastases and hemangiomas were significantly different regarding their means; however, they showed overlap to some extent.

The diffusion capacity of fat is reported to be low leading to decreased ADC values. Reported values are 0.15–0.59×10^{-3} mm^2/s, which are considerably lower compared to other benign tissues. A possible explanation for this finding is that MR signals come primarily from lipid bound water protons, which have conceivably a more restricted mobility than unbound protons. In addition large, slowly diffusing triglyceride molecules have a low diffusion capacity, which also results in low ADC values [29–31].

In this study we had one case of lipoma revealed signal void on both DWI and ADC maps, its ADC value measures 0.1×10^{-3} mm^2/s, and it was similar to that of malignant lesions, but lipoma can be easily differentiated depending on its signal appearance on different MRI sequences.

Previous studies reported variable ADC cutoff values for discrimination between malignant and benign hepatic focal lesions. Abdel Latif et al. [16], in their study used 1.0×10^{-3} mm^2/s as an ADC cutoff value at b 1000 resulted in 90.3% sensitivity, 78.6% specificity and 86.7% accuracy and they stated that the preferable results were obtained with ADC cutoff value of 1.5×10^{-3} mm^2/s (at b 500) and 1.0×10^{-3} mm^2/s ADC cutoff value (at b 1000), with 90.3% sensitivity, 92.86% specificity, and 91.1% accuracy. Taouli et al. [18] use a cutoff value of 1.5×10^{-3} mm^2/s at b 500 and they record a sensitivity of 84% and specificity of 89%. Parikh et al. [8] in their study reported 1.6×10^{-3} mm^2/s as a cutoff value at b 500 gradient and had sensitivity of 74.2% and specificity of 77.3%. And Onur et al. [32] stated a cutoff value of 1.23×10^{-3} mm^2/s at b 1000 with sensitivity of 83% and specificity of 76% for differentiation between benign and malignant lesions.

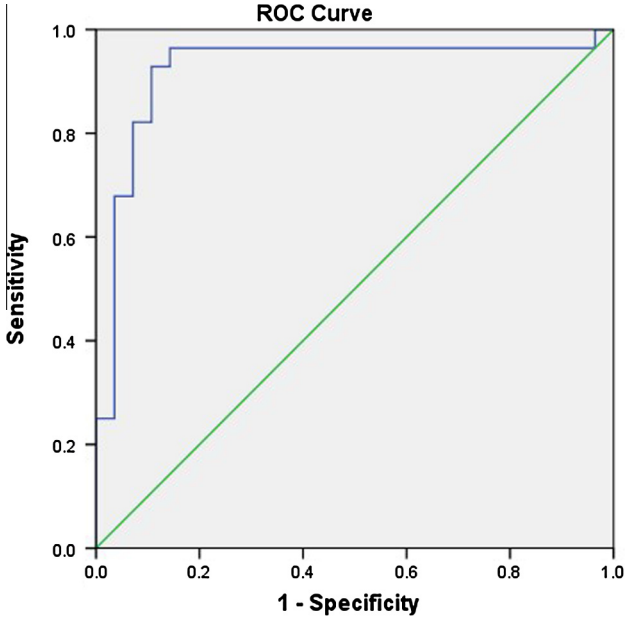

Fig. 6. Receiver operating characteristic curves for ADC value for differentiation between malignant and benign solid hepatic masses.

In this study we achieve nearly the same results as previous studies when we used an ADC value of 1.6×10^{-3} mm^2/s as cutoff value at *b* 1000 that results in 92% sensitivity, 80% specificity, 98% PPV, 50% NPV and 91% accuracy with AUC 0.90.

We had several limitations in our study as small number of the lesions were in each group especially in the benign lesions; we had only two benign entities: hemangioma and lipoma; and also IV contrast could not be used due to the impaired renal functions of patients included in our study.

5. Conclusion

From this study we concluded that the use of contrast materials is no longer needed in characterization of solid focal liver lesions, especially in patients with impaired renal functions, as DW-MRI and ADC value measurements are proved to be effective techniques with high sensitivity and accuracy in characterizing these lesions.

Conflict of interest

The authors declare that there are no conflict of interests.

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