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Role of Dynamic CE-MRI and DWI in Characterization of Hypervascular Focal Hepatic Lesions in Cirrhotic Liver

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Abstract

Background: Various types of hypervascular lesions are commonly found among patients with liver cirrhosis, however differentiating between benign and malignant hypervascular lesions in liver cirrhosis remains a key problem in the care of individuals at risk for developing hepatocellular carcinoma.

Patients with cirrhotic liver disease are always submitted to a regular check-up by abdominal ultrasound (US) for screening of hepatic focal lesions, if present triphasic CT scan is done to assess the pattern of enhancement as a reflection of its source of vascularity. A variety of hypervascular lesions can occur in cirrhotic liver, other than hepatocellular carcinoma (HCC), such as hemangiomas, focal nodular hyperplasia, intrahepatic cholangiocarcinoma, metastases or pseudo-lesions, such as perfusion anomalies, focal confluent fibrosis.

While the primary concern of a radiologist is to avoid a false negative diagnosis of malignant hepatic focal lesions as benign lesions, decreasing false positive diagnosis is also of the same value in order to decrease tumor over diagnosis.

Depending on triphasic CT or abdominal ultrasound in such lesions' differentiation is not always sufficient. Better tissue characterization by different MRI sequences including the diffusion sequences, apparent diffusion coefficient (ADC) values, and pattern of enhancement are highly recommended to avoid a false positive diagnosis of the arterially enhancing lesions for being HCC.

Aim of Study: To assess the role of the addition of dynamic CE-MRI and DW-MRI to the conventional MRI in better characterization of hypervascular hepatic focal lesions in cirrhotic liver, and to assess the benefits of the quantitative evaluation of ADC values in better characterization of the benign and malignant hypervascular hepatic focal lesions.

Patients and Methods: 25 cases of liver cirrhosis with 37 detected hepatic focal lesions, were examined with CT/US, if the final diagnosis was still hesitant a dynamic CE-MR was done, with DWI (b.0-500-1000) and their ADC maps were examined qualitatively and quantitatively by 2 experienced radiologists, (10 and 18 Yrs of experience. Results were recorded and ADC readings were analyzed on the ROC curve. The final results were diagnosed according to the standard of reference.

Results: There was a statistically significant difference between benign and malignant ADC values, with a *p*-value of 0.003. A suggested cut-off value was 1.525 have resulted in 89% accuracy. While reading the dynamic contrast-enhanced MRI we have reached a diagnostic accuracy of 72.9%, however, while reading the DWI and their ADC maps qualitatively we have reached 97.5%.

Conclusion: Conventional MRI sequences combined with dynamic CE-MRI and DWI provide a more accurate diagnosis for hypervascular hepatic focal lesions. The qualitative assessment of the DWI and their ADC maps, per se, have similar overall accuracy, and can be used without the CE-MRI sequences especially when it is contraindicated or not available. The quantitative ADC values were less accurate than the qualitative assessment of DW sequences. The higher the *b* value the better the detection of small malignant hepatic focal lesions, with less false negative lesions.

Key Words: *Hypervascular focal lesions – Hepatocellular carcinoma – Liver cirrhosis – Magnetic resonance imaging – CE-MRI, DWI.*

Introduction

PATIENTS with cirrhotic liver disease are always submitted to a regular check-up by abdominal ultrasound for screening of hepatic focal lesions,

Abbreviations:

US	: Ultrasound.
CT	: Computed tomography.
HCC	: Hepatocellular carcinoma.
MRI	: Magnetic resonance imaging.
ADC	: Apparent diffusion coefficient.
CE-MRI	: Contrast enhanced magnetic resonance imaging.
DW-MRI	: Diffusion weighted magnetic resonance imaging.
TACE	: Tumour ablation transarterial chemoembolization.
SOR	: Standard of reference.
RF	: Radio frequency.
MDT	: Multidisciplinary team.
CCA	: Cholangiocarcinoma.

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if present triphasic CT scan is done to assess the pattern of enhancement as a reflection of its source of vascularity. A variety of hypervascular lesions can occur in cirrhotic liver, other than HCC, such as hemangiomas, focal nodular hyperplasia, intrahepatic cholangiocarcinoma, metastases or pseudo lesions, such as perfusion anomalies, focal confluent fibrosis **[1]**. The differentiation between malignant and benign hypervascular lesions in patients with liver cirrhosis who are at risk for developing hepatocellular carcinoma remains a key difficulty [2].

While the primary concern of a radiologist is to avoid a false negative diagnosis of malignant hepatic focal lesions as benign lesions, decreasing false positive diagnosis is also of the same value in order to decrease the tumour over diagnosis, and hence putting the efforts and expenses of treatment such as tumour ablation transarterial chemoembolization (TACE) or liver transplantation to whom they are in need, with better cost-effective values **[1]**.

Depending on triphasic CT or abdominal ultrasound in such lesions' differentiation is not always sufficient. Better tissue characterization by different MR sequences including the diffusion sequences, ADC values, and pattern of enhancement are highly recommended to avoid a false positive diagnosis of the arterially enhancing lesions for being HCC [3].

Many studies have compared MR imaging and CT in depicting HCC in the cirrhotic liver, several studies found them comparable, while others have reported that MRI is more specific than CT (70% versus 50%, respectively) **[4]**.

Previous studies have examined the efficacy of DW MRI in diagnosing liver masses. Also, the appropriate technical parameters for hepatic lesions are unclear, as different investigations have generated DW images with different *b* values **[5]**.

The apparent diffusion coefficient (ADC) value used for quantitative analysis of hepatic lesions, have no cut-off point, hence there is no consensus on its routine usage for neoplastic lesion detection **[6]**.

Aim of work: To assess the role of the addition of dynamic CE-MRI and DW-MRI to the conventional MRI in better characterization of hypervascular hepatic focal lesions in cirrhotic liver, and to assess the benefits of the quantitative evaluation of ADC values in better characterization of the benign and malignant hypervascular hepatic focal lesions.

Patients and Methods

Study population:

This was a prospective study carried on Twenty five patients referred to our radiology department from the gastroenterology department for dynamic MRI at Kasr El-Aini Hospitals Cairo University between January 2018 and June 2018, proved by ultrasound examination to have hepatic focal lesions on top of cirrhosis followed by triphasic CT which was not conclusive. These 25 patients were 10 males and 15 females having a total of 37 focal lesions. The study was approved by the ethics committee of our institution.

Inclusion criteria:

All patients were known to have liver cirrhosis with hypervascular focal liver lesions detected by triphasic CT scan and need better characterization by dynamic contrast-enhanced MRI.

Exclusion criteria:

Patients refusing or having contraindications to the CE-MRI examination like cardiac pace makers, metallic foreign body, or impaired renal functions.

Methods:

Combined abdominal MRI was done (dynamic pre- and post-contrast study-arterial, portal, and delayed venous phases, as well as diffusion-weighted imaging), followed by three phases of readings which were blinded to the Triphasic CT findings; first, blind characterization and detection of focal lesions were performed to the conventional MR sequences, second, the diffusion images with the ADC values of the detected focal lesions were reviewed without viewing the post Gadolinium sequences and third characterization of the pattern of enhancement of the different focal lesions in the arterial, portal and delayed phases. The results were compared to laboratory findings, and other previous radiological (US and/or MSCT) findings done for all patients. The final diagnosis was achieved according to the standard of reference (SOR) **[7]**.

MRI examination:
The Machine:

We used (1.5 Tesla) MRI machine, “Philips Intera and Achieva” using a phased array, 4 quadrature coil channels plus 1 linear channel. This MRI system employs the Synergy RF system, which manages a mix of 4 quadrature coil channels

and 1 linear channel, with the capability of simultaneously connecting several coils to cover the entire liver.

Patient preparation:

- Fasting for 4-6 hours before the scan.
- Metallic objects were taken off before the examination.

Patient position:

Supine, head first, with arms raised above the head.

Pulse sequences:

Precontrast routine MRI of the abdomen followed by DWI using the scan parameters as shown in the following (Table 1):

Table (1): Scan parameters of the different sequences of routine precontrast MRI of the abdomen.

	TR/TE	Matrix	Slice thickness	Gap	FOV	NEX	Plane
T1WI	10/4.58 msec	179x320	7mm	1mm	355		Axial
T2WI	445/26 msec	200x240	7mm	1mm	365		Axial
T2 SPAIR FS	400/80msec	204x384	7mm	1mm	365		Axial
Dual in/out phase	75/4.6msec in phase	143x240	7mm	0mm	345		Coronal
	75/2.3msec out phase						
Long T2WI	520/200msec	235/384	7mm	1mm	375		Axial
DWI	1880/70 msec	256x256	7mm	1mm	52%	3	Axial
b 0,500,1000							

Dynamic study:

A bolus of (0.1mmol/kg) Gd-DTPA is injected in the antecubital vein, followed by 20mm of saline at a rate of 2ml/s.

A pre-contrast T1 THRIVE (High-Resolution Isotropic Volume Examination) was taken before injection followed by three scans of the liver after 20, 60, and 180 sec from the start of contrast injection.

Imaging analysis:

Image analysis was obtained by two radiologists (5 and 15 years) experience, the latter has experience in the gastroenterology and hepatobiliary subspeciality. They were not aware with the Triphasic CT results and the final diagnosis of the patient. First, the morphological features were recorded for each lesion including size, margin, shape, signal pattern, as well as the site and the number of the hepatic focal lesions. Second, the diffusion images, of the different b values with their ADC maps were reviewed qualitatively, before viewing the dynamic post-contrast series. The mean ADC values were measured twice for each detected focal lesion, by drawing a region of interest over the lesion and getting the average of the two measurements. Regions of interest (ROI) were replicated from DWI to ADC maps to ensure that the same areas were measured. Then provisional diagnosis was reported. Third, identification of the enhancement pattern of the focal lesions in the arterial, portal and delayed phases.

Post-processing image subtraction was done on workstation using the software subtraction function for lesions with bright T1 WI signal in the pre-contrast images to evaluate the true contrast uptake in the post-contrast images.

All the obtained results were compared in order to reach the final diagnosis which was correlated with the clinic-laboratory findings in a multidisciplinary team MDT meeting according the Standard of reference (SOR):

A variety of techniques have been recognized as "gold standards" for the characterization of lesions [7].

HCC were diagnosed when there were a neoplastic pattern of enhancement on cross sectional images and elevated α-fetoprotein. Hemangiomas were diagnosed when they were echogenic by US and/or the characteristic enhancement pattern of peripheral nodular enhancement and fill-in in the delayed phase, if still in doubt; follow-up of the size of the mass on subsequent radiological examinations.

For the metastatic foci, the patients were known to have multiple hepatic focal lesions and primary malignancy (pancreatic and colon cancer), that were either co-incident ornewly developed during routine screening. A biopsy was done if suspicious.

Patients with intrahepatic cholangiocarcinoma (CCA) were suspected by imaging criteria and clinical conditions of the patients, followed by

tumour carbohydrate antigen 19-9 serum marker and biopsy if inoperable or surgery and pathological examination if operable [8].

Statistical analysis:

When appropriate, data were statistically reported in terms of mean, standard deviation (SD), median, and range. Mann Whitney U test for independent samples was used to compare the ADC between normal and malignant tumours. Sensitivity and specificity represented accuracy. ROC analysis determined the best ADC cut-off value for malignancy diagnosis. Statistical significance was 0.05 or less. IBM SPSS release 22 for Microsoft Windows performed all statistical calculations.

Results

Demographic data:

The study included twenty-five patients with liver cirrhosis, (10-40%) males (15-60%) females. The patients' ages were ranging from 12 to 69 years with a mean age of 54.2 years.

There were 37 hypervascular hepatic focal lesions detected in the overall 25 patients. All the lesions were found in the post-HCV cirrhotic liver. The number of different pathological lesions and their sizes are mentioned in (Tables 2,3), as diagnosed by the standard of reference (SOR).

Table (2): Number of different pathological lesions.

The pathological lesions	Number of the lesions
HCCs nodules	16
High grade dysplastic nodules	2
Hemangioma	6
Cholangiocarcinoma	2
Metastatic	10
Confluent hepatic fibrosis	1
Total	37

Table (3): Demonstrates the number of lesions according to their sizes.

Size of lesions (cm)	Number
0.5-1	10
1.1-2	10
2.1-5	14
5.1-10	2
>10	1

Analysis of the obtained data:

The number of focal liver lesions, diffusion pattern, ADC value, arterial enhancement, and washout as well as the final diagnosis according to the standard of reference (SOR), for each case are mentioned in (Table 4).

The distribution of the benign and malignant lesions according to the different dynamic CE-MRI sequences. (Dynamic CE-MRI, qualitative diffusion, ADC with 1.525 cut-off values) are shown in (Table 5).

The Diagnostic indices of the different dynamic MRI sequences. (Dynamic CE-MRI, qualitative diffusion, and ADC with 1.525 cut-off value) (Table 6).

Analysis of results according to the dynamic CE-MRI findings:

From the 16 hepatic focal lesions which were diagnosed as HCC, (were diagnosed by typical imaging criteria in accordance with the American association of the study of liver disease) (AASLD); 15 lesions displayed early arterial enhancement and washout of the contrast in the portal & delayed phases, while one focal lesion showed arterial enhancement with persistent contrast uptake in the early portal phase. Among those 16 HCCs, there was one case that showed a well-ablated focal lesion but with the development of a new lesion.

There were two small high-grade dysplastic nodules that showed relative arterial enhancement and washout in the portal-venous phase. (They had bright T1WI signals).

The diagnosis of the 2 cholangiocarcinomas was depending on the clinical conditions of the patients, and the laboratory findings of elevated tumour carbohydrate antigen 19-9 serum marker and by abdominal U/S, they showed large heterogeneous mass lesions. Further MRI study revealed a large heterogeneous enhancing mass with contrast filling in one lesion and washout in the other lesion. The lesions were also associated with biliary radicle dilatation, and capsular retraction. They were operated upon and pathologically proved as intrahepatic cholangiocarcinomas.

The metastatic patients had a total of ten hepatic focal lesions and primary malignancy (pancreatic and colon cancer), that were either co-incident or newly developed during routine screening. One case with four lesions showed thick marginal arterial enhancement with relative washout in the delayed venous phases. Another case with four focal lesions showed late arterial enhancement with persistent contrast uptake and a third case with two focal lesions showed no arterial enhancement or was hout representing cystic areas of breakdown.

Table (4): The number of lesions, diffusion pattern, ADC value, arterial enhancement, and washout as well as the final diagnosis according to the standard of reference (SOR) for each case.

No.	Cases	Lesions	DWI	ADC value 1.525	Arterial enhancement	Washout in portal and delayed venous phase	Final diagnosis according to the SOR.
1	1	2	f	1.58	+	–	Hemangioma
2	1		f	1.58	+	–	Hemangioma
3	2	Multiple(4)	R	1.84	+	–	Metastasis
4	2		R	1.84	+	–	Metastasis
5	2		R	1.84	+	–	Metastasis
6	2		R	1.84	+	–	Metastasis
7	3	1	R	1.06	+	+	HCC
8	4	1	f	1.89	+	–	Hemangioma
9	5	1	R	1.24	+	–	HCC
10	6	3	f	1.54	+	–	Hemangiomata
11	6		f	1.54	+	–	Hemangiomata
12	6		f	1.54	+	–	Hemangiomata
13	7	1	R	1.34	+	+	cholangiocarcinoma
14	8	1	R	1.22	+	+	Hcc (recurrenc
15	9	1	R	1.09	+	+	HCC
16	10	2	R	1.30	–	–	Metastasis
17	10		R	1.30	–	–	Metastasis
18	11	1	R	1.2	+	+	HCC
19	12	1	R	1.23	+	–	Cholangiocarcinoma
20	13	1	R	1.32	+	–	Confluent hepatic fibrosis
					Faint	Delayed enhancement	
21	14	4	R	1.22	+	+	Metastasis
22	14		R	1.22	+	+	Metastasis
23	14		R	1.22	+	+	Metastasis
24	14		R	1.22	+	+	Metastasis
25	15	1	R	1.13	+	+	HCC
26	16	1	R	1.18	+	+	HCC
27	17	1	R	1.42	+	+	Early HCC
28	17	1	R	1.12	+	–	High grade D.N.
29	18	1	R	1.17	+	+	HCC
30	19	1	R	1.31	+	+	HCC
31	20	1	R	1.14	+	+	HCC
32	21	1	R	1.51	+	+	HCC
33	22	1	R	1.33	+	+	HCC
34	23	1	R	1.15	+	+	HCC
35	24	2	R	1.06	+	+	HCC
36	24		R	1.06	+	+	HCC
37	25	1	R	1.12	+	–	High grade D.N.

NB: A positive case for malignancy is having +Ve arterial enhancement and +ve washout.

Table (5): Distribution of the benign and malignant lesions according to the different dynamic MRI sequences. (Dynamic contrast MRI, qualitative diffusion, ADC with 1.315 and 1.525 cut-off values).

Pathology	SOR		Dynamic CE-MRI		Qualitative diffusion		Quantitative diffusion ADC cut-off=1.525	
	N	%	N	%	N	%	N	%
Malignant hepatic focal lesions	30	81	20	54	31	84	26	70
Benign hepatic focal lesions	7	91	17	46	6	16	11	30

Table (6): Diagnostic indices of the different dynamic MRI sequences. (Dynamic contrast MRI, qualitative diffusion, ADC value with 1.525 cut-off values).

Diagnostic indices of	Dynamic contrast MRI	Qualitative diffusion	Quantitative diffusion ADC cut-off=1.525
Sensitivity	66.6%	100%	86.6%
Specificity	100%	85.7%	100%
Positive predictive value (PPV)	100%	96.7%	100%
Negative predictive value (NPV)	41.1%	100%	63.6%
Acuracy	72.9%	7.3%	89.1%

The 6 hemangiomata lesions were accidentally discovered during abdominal U/S performed for routine follow-up of cirrhotic patients. Further MRI evaluation was done to be sure of the diagnosis with the aid of their enhancement pattern and their diffusion pattern.

One lesion was finally diagnosed as focal confluent hepatic fibrosis, for its triangular shape with mild capsular retraction, moreover, it showed faint early and delayed contrast enhancement in the arterial and delayed phases respectively.

While comparing the results of dynamic MRI to the standard of reference, (considering an arterial enhancement and portovenous washout as malignant), there was a 66.6% sensitivity, 100% specificity, 100% PPV, 41% NPV, and overall accuracy 72.9% (Table 6).

Analysis of results according to the diffusion MRI and ADC number:

Finally the diffusion images of the focal lesions with different *b* values (0, 500, 1000) and their ADC values were evaluated for final radiological characterization.

All hemangiomata lesions exhibited facilitated diffusion, as evidenced by a decrease in signal intensity with rising *b*-values, (lesions with T2 shine through effect -those that did not exhibit a decrease in signal intensity and had a high signal on the ADC map - were judged to exhibit free diffusion). On the other hand all solid lesions including the focal confluent hepatic fibrosis case showed restricted diffusion (persistent high signal with the 500 and 1000 *b*-values and corresponding low signal on ADC maps).

When considering the qualitative assessment of the diffusion images by looking at the different 0,500 and 1000 *b* values, and the ADC map signal, we have reached (100% sensitivity, 85.7% specificity, 96.7% PPV, 100% NPV, and 97.3% overall accuracy. (Table 6).

ADC values were obtained for the 37 focal liver lesions (7 benign and 30 malignant). The mean ADC value of the different hepatic focal lesions detected, by their final suggested diagnosis according to the SOR. (Table 7).

The mean ADC value of the malignant lesions was 1.30±0.24x10-3mm^2/sec, and of the benign lesions was 1.57±0.17x10-3mm^2/sec with a statistically significant difference, *p*-value = 0.003. (Table 8).

After reading the ADC values on the ROC curve considering the malignant lesions as positive, there was a suggestion of a cut-off equal to or less than 1.525, denoting malignancy. With a resultant 86.6% sensitivity, 100% specificity, 100% PPV and 63.6% NPV, and 89.1% accuracy. (Table 6).

Table (7): Mean ADC value of the different lesions.

Lesion type	Mean ADC value (mm^2/sec)
Hemangioma	1.6±0.14x10^{-3}
Confluent fibrosis	1.32x 10^{-3}
High grade dysplastic nodules	1.12x 10^{-3}
HCC	1.18±0.12x 10^{-3}
Cholangiocarcinoma	1.28±0.08x10^{-3}
Metastasis	1.48±0.31 x 10^{-3}

Table (8): ADC values among 7 benign and 30 malignant hepatic focal lesions.

Pathology	N	ADC value			*p*-value
		Mean ± Std. Deviation	Range	Median	
Malignant hepatic focal lesions	30	1.30±0.24x 10^{-3}mm^2/sec	(1.06-1.84) 10^{-3}mm^2/sec	1.22 x10^{-3}mm^2/sec	<0.003
Benign hepatic focal lesions	7	1.57±0.17x 10^{-3}mm^2/sec	(1.32-1.89) 10^{-3}mm^2/sec	1.54 x 10^{-3}mm^2/sec	

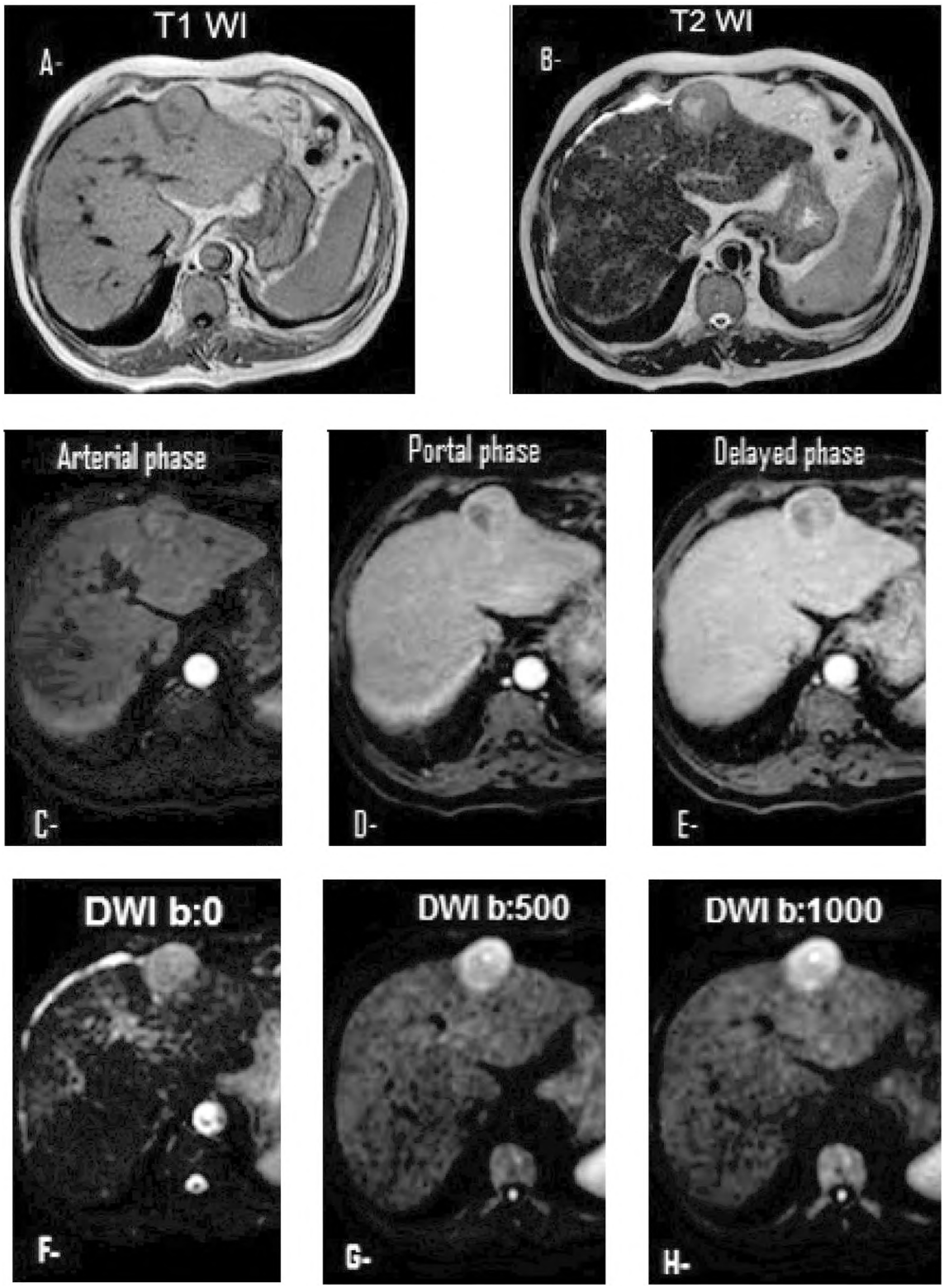

Fig (1): (A-H): 65 year old male patient presented with abdominal pain mainly at the right hypochondrial region. AFP was 625ng/ml. Dynamic MRI study revealed typical hepato-cellular carcinoma. Axial unenhanceded T1W I (A) and T2WI (B) showed a left hepatic lobe mass lesion of mixed iso and low signal intensity on T1 WI and mixed iso and high signal intensity on T2WI image. Axial gadolinium-enhanced arterial-phase image (C), portal phase (D) and delayed venous phase (E), showed early enhancement of the lesion in the arterial phase and rapid washout in the portal and delayed phases with persistent capsular enhancement in the delayed venous phase. On DWI (b: 0,500, 1000) (F, G and H) respectively; showed increase in the signal intensity (diffusion restriction) by increasing the b value. Axial ADC map (not shown) showed the lesion to be of decreased signal intensity, with ADC value was 1.06×10^{-3} mm^2/sec. proving that the high signal intensity on DWI was not T2 shine-through effect, but a truly restricted diffusion.

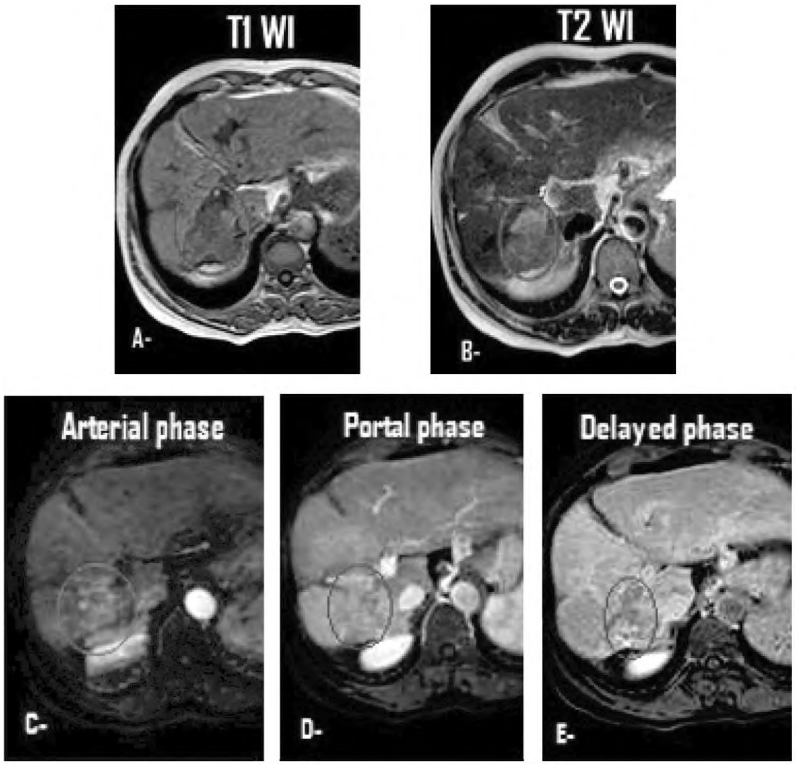

Fig (2): (A-E): 64 year old female patient having past history of HCC segment VIII treated with TACE, presented with abdominal pain, mild jaundice and loss of weight, AFP: 1264ng/ml, dynamic MRI revealed typical hepatocellular carcinoma with portal vein invasion (red circle). Axial unenhanceded T1WI (A) and T2WI (B) showed a large posterior segment, right hepatic lobe focal lesion of low signal intensity on T1WI and high signal intensity on T2WI. Axial gadolinium-enhanced arterial-phase image (C), portal phase (D) and delayed venous phase (E), showed an ill-defined infiltrative mass invading and obliterating the right portal vein by a heterogeneously enhancement in the arterial phase and contrast washout in the portal and delayed phases.

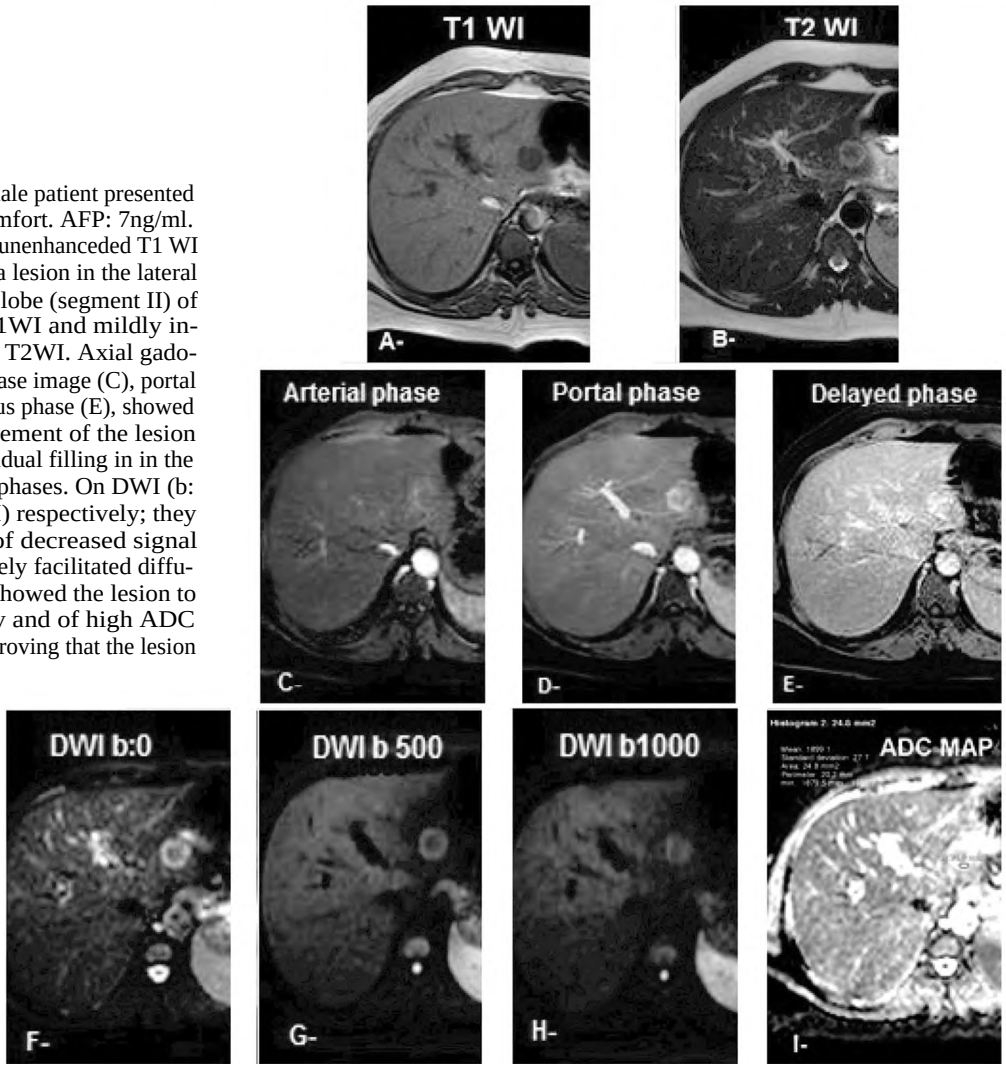

Fig. (3): 52 year old female patient presented with mild abdominal discomfort. AFP: 7ng/ml. Typical hemangioma. Axial unenhanceded T1 WI (A) and T2WI (B) showed a lesion in the lateral segment of the left hepatic lobe (segment II) of low signal intensity on T1WI and mildly increased signal intensity on T2WI. Axial gadolinium-enhanced arterial-phase image (C), portal phase (D) and delayed venous phase (E), showed peripheral nodular enhancement of the lesion in the arterial phase and gradual filling in in the portal and delayed venous phases. On DWI (b: 0, 500, 1000). (F, G and H) respectively; they showed the lesion to be of decreased signal intensity owing to more likely facilitated diffusion. Axial ADC map (I) showed the lesion to be of high signal intensity and of high ADC value ($1.6x10^{-3}$ mm^2/sec), proving that the lesion is of benign nature.

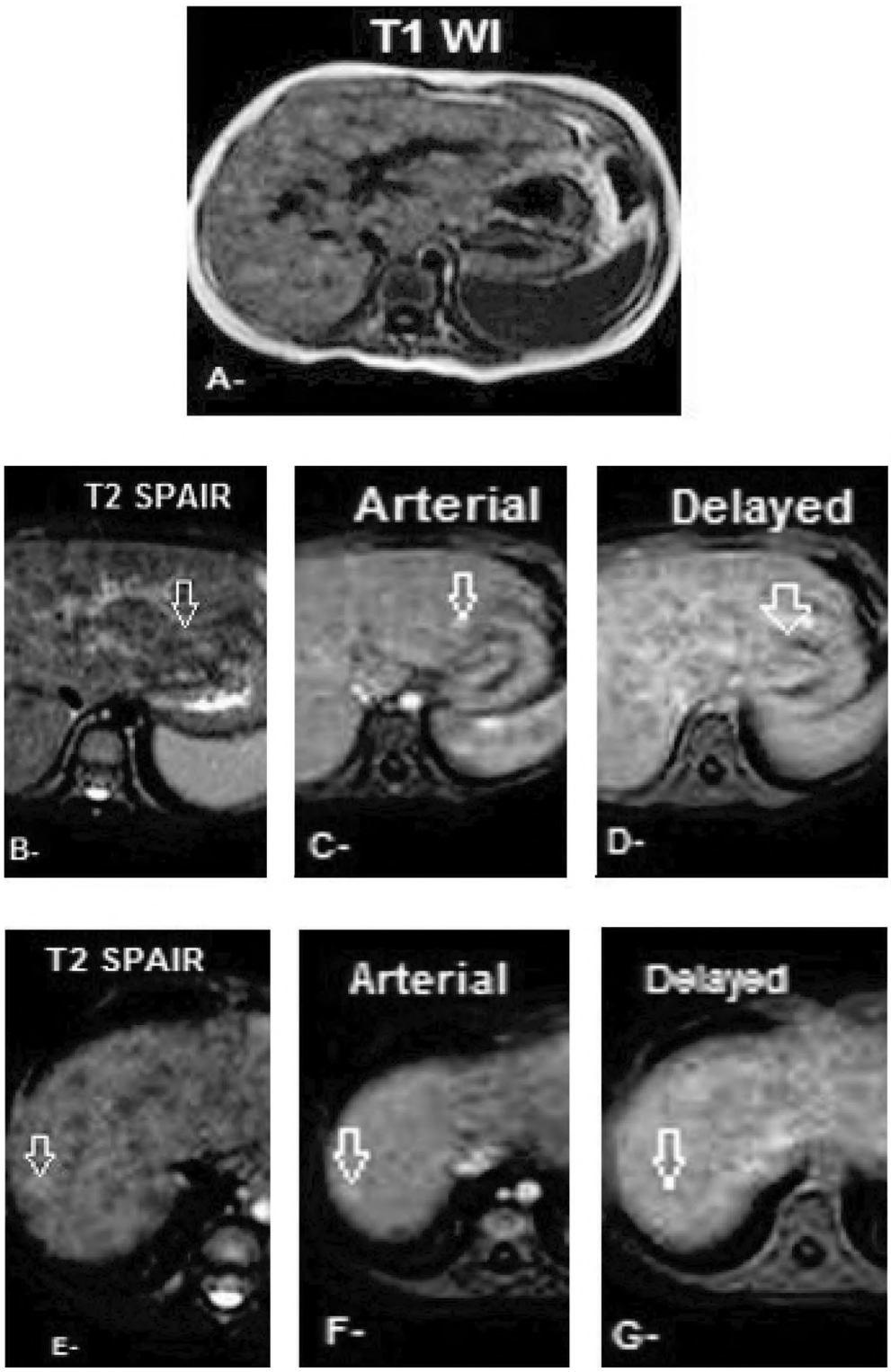

Fig. (4): 12 years-old child female patient is coming for MRI characterization of multiple innumerable focal hepatic lesions detected at U/S). Dynamic MRI revealed early HCC and high-grade dysplastic nodule. Axial unenhanceded T 1 WI (A) images showed multiple hyperintense scattered nodules in both liver lobes. Axial T2 SPAIR, arterial and delayed images for a segment III hepatic focal lesion, (B, C and D) respectively, showed low T2 SPAIR signal intensity with a peripheral anterior high signal lesion, the latter part shows arterial enhancement and wash out in the delayed phase. (early HCC) Axial T2 SPAIR, arterial and delayed images for a segment VII focal lesion, (E, F and G) showed slightly high T2SPAIR signal intensity, with faint arterial enhancement but with no significant washout in the delayed phase (high grade dysplastic nodule).

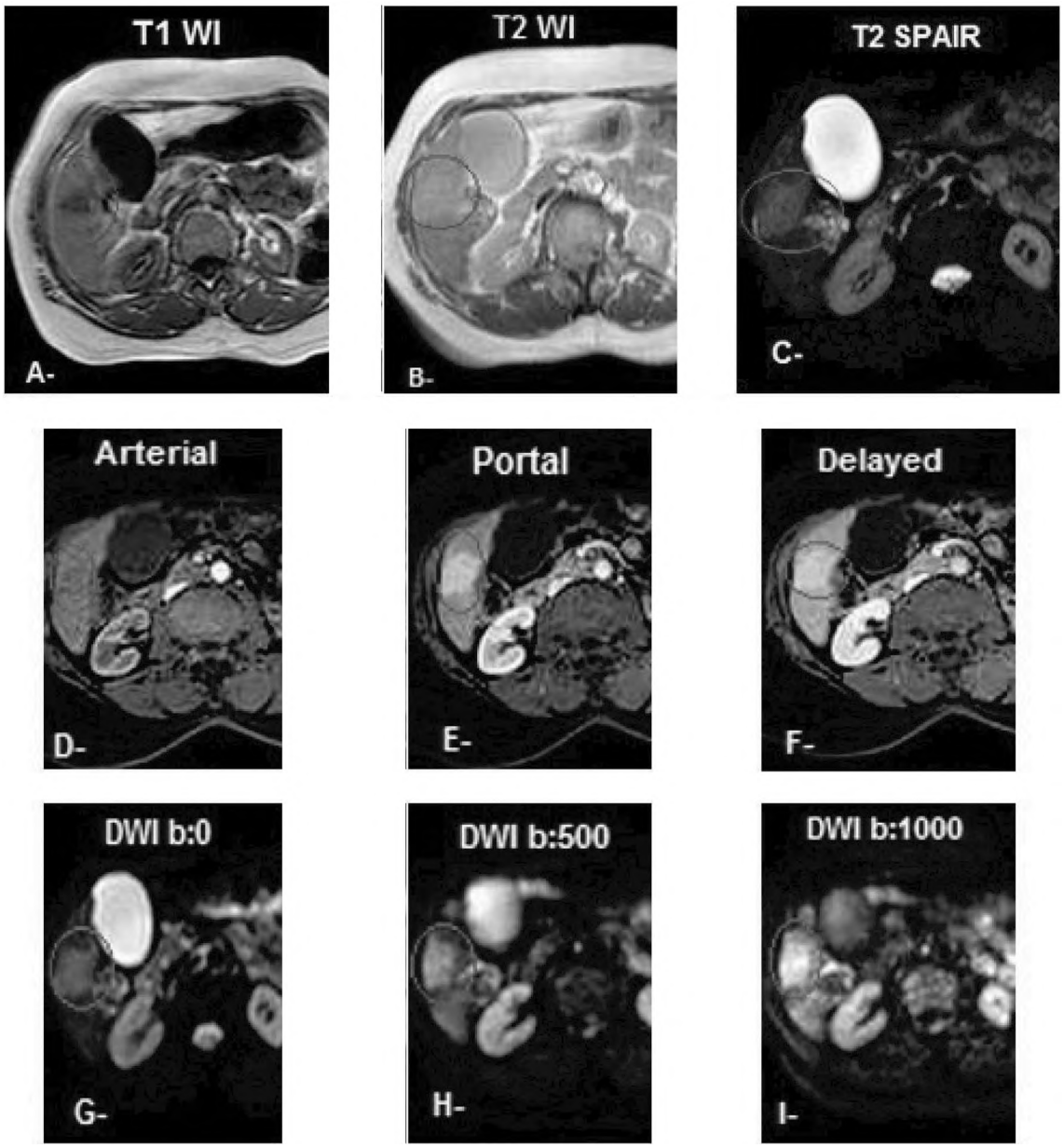

Fig. (5): 58 year old female patient presented with mild abdominal pain. AFP: 4ng/ml. Dynamic MRI revealed confluent hepatic fibrosis (red circles). Axial unenhanceded T1WI (A), T2WI (B) and T2SPAIR (C), shows patchy wedge-shaped area of low signal intensity at right lobe of the liver, (segment V) having hypointense T1WI, bright T2WI and T2 SPAIR images Axial T1-weighted spoiled gradient-echo MR im-age obtained in the arterial phase, (D), portal phase (E) and delayed venous phase (F) showed no significant enhancement of the lesion in the arterial phase, with delayed enhancement in the portal and delayed phases, a characteristic finding of fibrosis. Capsular retraction secondary to subtle volume loss is also seen. (best seen in the dynamic phases). The ADC value (not shown) was $1.32X10^{-3}$.

Discussion

According to the European Association for the Study of the Liver (EASL) focal lesions of the liver are diagnosed by ultrasonography and/or computed tomography, then further characterization is done by MRI. Acording to Caraiani, 2015 the MRI is better in detection of HCC in cirrhotic liver as compared to CT and US, with a detection rate of 72%, 65% and 48% respectively **[9,10]**.

Numerous advantages of magnetic resonance imaging (e.g. the capacity to get images in any plane, high contrast resolution, avoidance of ionising radiation. It could be the first line of assessment in case of suspicion of a benign lesion, and it could reach a final diagnosis in conjunction with the patients' history and laboratory findings, to be able to put a management plan. However, in case of doubt, a biopsy or resection would be important after a multidisciplinary team consideration, in order not to miss a malignancy **[9]**.

While dynamic contrast-enhanced MRI is used to diagnose a variety of liver disorders, including hepatic focal lesions **[11]**, diffusion-weighted imaging (DWI) of the liver is a non-contrast sequence that became routinely performed on most commercial devices. Its excellent contrast resolution allows accurate FLL detection and characterization **[10]**, **[12,13]**. It can obtain functional information without a need for intravenous contrast, making it safe for patients with renal function abnormalities. It helps distinguish benign and malignant focal hepatic lesions by qualitative and quantitative evaluation **[11]**.

The current study had 25 cases having cirrhotic liver with 37 hepatic focal lesions, they were examined by dynamic CE-MRI with DWI, the diffusion sequences, were evaluated qualitatively with their (b. 0, 500, 1000 and ADC map signal) and quantitatively with their ADC value.

According to Galia et al., **[1]** and Gaurav et al., **[14]** the pattern of enhancement in the multiphasic MRI helps in characterizing the hepatic focal lesions, for example HCC tumour shows enhancement during the hepatic arterial phase followed by washout during the venous and delayed phases. However, in a small HCC, the washout may not occur as the portal blood supply will still be intact. In this dynamic study, (15/16-93.7%) lesions of HCC, that exhibited the characteristic early arterial contrast uptake with a portal and delayed phases washout and persistently delayed enhancement of the outer rim "capsule". (Fig. 1-D,E). Only one out of the 16 HCCs showed early arterial enhancement without washout (remained bright in relation to liver parenchyma) on venous and delayed phases. (Case 5 in Table 4).

Gaurav et al. (20 10) found that malignant portal vein thrombosis in HCC ranges from 5% to 44% and has the same signal intensity and contrast enhancement pattern as the underlying tumour. Two HCC tumours had portal vein invasion in this study. (Fig. 2-C,D,E).

According to Galia et al., **[1]**; the most common malignant lesion that occurs on top of liver cirrhosis is the small HCC followed by small cholangiocarcinoma, the latter will typically be hypervascular if less than 3cm, which makes it difficult to be differentiated from the small HCCs. A large cholangiocarcinoma (>3cm) will have its typically enhancing peripheral rim with centripetal filling, capsular retraction, and small localized areas of ductal dilatation. There were two pathologically proven cholangiocarcinomas in the current study, they had a typical arterial enhancement, one of them showed delayed fill in and the other showed washout in the venous phase.

According to Schima et al., **[15]**, most of the hepatic metastases are enhancing in the portal phase, however hypervascular metastatic lesions that enhance in the arterial phase are breast carcinoma, neuroendocrine tumours, renal cell carcinoma, and sarcomas, usually become isointense to the liver parenchyma in the portal phase, making them hard to detect. Some metastasis may show peripheral washout sign in the delayed images. In the current study, we had metastatic deposits from pancreatic and colon cancers. 4/10-40% of metastatic lesions showed thick marginal arterial enhancement with relative washout in the delayed venous phases, and 4/10-40% of metastatic lesions showed late arterial enhancement with persistent contrast uptake and 2/10-20% of metastatic lesions showed no arterial enhancement or washout representing cystic areas of breakdown.

According to Schima et al., **[15]**; a hemangioma usually appears as a flash filling matching with the aorta and the hepatic veins during the arterial and venous phases, respectively. However sometimes when it develops on top of underlying cirrhosis a hemangioma would be hypovascular due to the distorted liver parenchyma by a fibrotic process, in this case, the arterial flash filling will be absent, and an irregular hypoattenuating lesion will appear in relation to the surrounding liver parenchyma, during the arterial and delayed phases mimicking the hypovascular HCC, however the atypical hemangioma will be strongly hyperintense on T2WI. In this study, there were six cases of hemangioma, which were typical in appearance (Fig. 3).

According to Schima et al., **[15]**, the other benign lesions that would appear on top of cirrhosis are the focal nodular hyperplasia, regeneration nodules, and dysplastic nodules. Dynamic CE-MR imaging improves the evaluation and characterization of hepatic focal lesions. In the current study; there was one case that showed multiple scattered regeneration nodules, two of these nodules showed late arterial enhancement and absent washout, features suggestive of high-grade dysplastic nodules. Dynamic CE-MR imaging helps discover worrisome nodules by detecting their enhancing pattern. (Fig. 4).

Diffusion-weighted imaging (DWI) of the liver is currently accepted and can be conducted on the majority of commercially available devices **[12]**.

It has a high contrast resolution allowing precise FLL detection and characterization without the need for intravenous contrast, which makes it suitable for patients with renal impairment **[10]**.

It is used as a complementary sequence to the routine MRI of the liver it provides qualitative and quantitative data for the focal liver lesions. Its principle is based on measuring the random motion of water into a voxel of tissue. It has higher sensitivity for detecting small focal lesions and it can depict the difference between normal parenchyma and malignant tissue cellularity **[10,11]**.

Çengel and Karahan, **[16]** have obtained DWI via a single-shot echo-planar imaging sequence with a parallel imaging approach in the axial plane, (b: 0-50-500-1000 s/mm^2) at the same level and orientation as the regular sequences. This technique is similar to that of the current study, as we have used similar image parameters and techniques while obtaining the diffusion sequences, using (b: 0-500-1000 s/mm^2) in order to increase the sensitivity to cellular packing.

Çengel and Karahan, **[16]** have compared the diagnostic indices of T2WI and signal characteristics of DWI ADC in distinguishing the benign from malignant lesions, they have found sensitivity, specificity, and accuracy for the DWI of 96%, 85%, and 88%. In the current study we have done a qualitative assessment of the diffusion images by looking at the different 0,500 and 1000 *b* values, and their ADC we have reached (100% sensitivity, 85.7% specificity, 96.7% PPV, 100% NPV, and 97.5% overall accuracy). This higher accuracy rate could be explained by the diagnostic methodology that has been used; we have revised the different *b*-values and their ADC, if the signal is decreasing while increasing the b-value with a corresponding bright signal on the ADC map it was considered facilitated, a T2 shine-through effect (those which didn't show a reduction of signal and showed high signal on ADC map) was also considered facilitated diffusion and a restricted diffusion was considered when there was an increase in the signal intensity while increasing the b-value with corresponding dark ADC map signal.

According to Shenoy-Bhangle et al. **[11]** who wrote in a review article that DWI with high b-values (b 100) helps in better detection of small lesions nearby the blood vessels as the higher the b value the higher the inhibition of the surrounding liver parenchyma, which helps in better lesion detectability, especially if there are surrounding arteries or if the lesion is in the periphery of the liver, which of much benefit in the detection of liver metastases. In the current study, we had 10 metastatic focal lesions, all of them showed restricted diffusion.

Shenoy-Bhangle et al. **[11]** have reported that DW-MRI alone is less sensitive than the hepatocyte-specific MRI contrast agent; gadoxetic acid-enhanced MRI for detecting liver metastases, but when paired with multiphase contrast enhanced MRI, its sensitivity increases from 90.6% to 95.5%. However we did not use hepatocyte specific contrasts in our study.

In the current study we have used Gadolinium-DTPA in the dynamic contrast-enhanced MRI of the liver, while considering the coincidence of an arterial enhancement and portal-venous washout as malignant, there was a 66.6% sensitivity, 100% specificity, 100% PPV, 41% NPV, and overall accuracy 72.9% however while considering a positive case for malignancy is the case that has a malignant pattern of enhancement and/or restricted diffusion as positive the diagnostic indices became (100% sensitivity, 85.7% specificity, 96.7% PPV, 100% NPV, and 97.5% overall accuracy). This is matching with Shenoy-Bhangle et al. **[11]**, as when adding the DWI qualitative results to the enhancement pattern of the lesion, the sensitivity and the NPV and total accuracy have much increased, and with Debees et al. **[17]** who concluded that the combination of Dynamic CE-MRI and DWI is sensitive for both differentiating between benign and malignant hepatic lesions and for the early detection of malignant neoplastic lesions.

Can we add DWI and ADC maps to conventional MRI without the need for the expenses of the dynamic Gadolinium CE-MRI?

In our study while considering the pattern of enhancement alone; (positive arterial enhancement and positive washout) there were 10 false negative cases, missing 6/10 metastatic lesions, 1/10 cholangiocarcinoma (as typically it does not washout), 2/10 high-grade dysplastic nodules, and 1/10 HCC, with relatively low total accuracy (72.9%), however, while considering a malignant case is the case that has post-GAD enhancement and /or the restricted diffusion we have got the same parameters as using the DW images and the ADC map qualitatively alone; reaching a total accuracy of (97.3%) with no false negative cases, which means that we did not miss any malignant lesions. Also we had only one false positive lesion, this lesion had a restricted diffusion but it was finally diagnosed as confluent hepatic fibrosis (benign). This

might be attributed to the selection of high b values, (b 500 and 1000), as concluded by (Dilek et al., 2019) **[18]** who have found that the higher the *b* value the better the detection of malignant lesions with a higher accuracy rate than the conventional T2W sequences. Our results agree with Elbarbary et al., 2014 **[19]** who concluded that when it comes to the detection and differentiation of various hepatic focal lesions, DW MRI alone performs on an equal level with Gd-MRI. A protocol based on unenhanced T1 and T2 weighted imaging in combination with DWI can be used to replace dynamic contrast-enhanced imaging in situations where gadolinium injection is not permitted. The accuracy of Gd-MRI is improved by DWI.

Is there an additive role of the quantitative ADC value of DWI in focal hepatic lesion characterization?

According to Hasan et al., 2016 **[6]**; malignant lesions had considerably lower mean ADC values (0.94±0.32x103 mm^2/s) than benign lesions (2.64 ±0.46x 103 mm^2/s) (P 0.001). Using an ADC value greater than 1.6x103 mm^2/s for benign lesions provided the highest accuracy (86%) in distinguishing malignant from benign lesions. The quantitative assessment of the ADC map was more accurate (87.5%) than the qualitative assessment of DWI (75%).

This study the mean ADC values of malignant lesions (1.30±0.24x10-3mm^2/sec) were significantly lower than those of benign lesions (1.57±0.17 x10-3mm^2/sec), (p<0.003). we have put the ADC numbers of the ROC curve, while considering malignant lesion is the positive variant, there was a statistically significant difference with p-value 0.003, the results that gave the best sensitivity for the detection of malignant lesions was less than 1.525, while using 1.525 as the cut-off value we got 86.6% sensitivity, 100% specificity, 100% PPV and 63.6% NPV, and 89% accuracy. These results were less than the accuracy of the qualitative diffusion which is 97.5%, this agrees in a way with Caraiani et al., **[10]** as they evaluated DW b-800, and its ADC map qualitatively then they compared two ways for the quantitative assessment first the ADC value and second the ADC ratio, (between the ADC number in the focal lesions and the ADC number in the normal liver parenchyma). They have reported that the latter had better sensitivity and specificity in the diagnosis of malignant focal lesions. In our study, we did not measure the ADC ratio, yet our data were matching with them as the qualitative assessment is depending on the visual comparison of the intensity of the lesion as compared to the rest of the liver parenchyma. We recommend a further study that puts the ADC ratio into consideration.

Concerning the quantitative assessment of the ADC values, the threshold values for differentiating benign from malignant focal lesions vary between studies depending on the utilized MRI parameters and the diffusion gradient strength. According to scientific literature, there is a lot of overlap between malignant liver lesions like hepatocellular carcinoma and metastases and benign hyper cellular liver lesions such localized nodular hyperplasia and hepatic adenomas **[16,20,21]**.

The current study did not have FNH or hepatic adenoma, so there was no significant overlap between the ADC values of the benign and malignant lesions.

We agree with Park HJ, et al., 2013, Wei et al., 2015, Lee et al., 2015,and Hasan et al., **[22-24]** and **[6]** who concluded that the use of absolute ADC values or ADC value cut-offs for characterizing focal hepatic lesions should be avoided, because of the considerable overlap of ADCs values between solid benign and malignant lesions. The DWI should be interpreted under guidance of the clinical data, and conventional MR sequences.

Limitations of the study:

The small number and variety of cases, as we have done the research in a short time and we have only included cases that failed to be diagnosed by ultrasound and/or Triphasic CT scan.

Conclusion:

Finally, we concluded that; conventional MRI sequences combined with dynamic CE-MRI and DWI provide a more accurate diagnosis for hypervascular hepatic focal lesions. The qualitative assessment of the DWI and their ADC maps, per se, have similar overall accuracy, to the dynamic CE-MRI and can be used without the CE-MRI sequences especially when it is contraindicated or not available. The quantitative ADC values were less accurate than the qualitative assessment of DW sequences. The higher the b value the better the detection of small malignant hepatic focal lesions, with fewer false negative lesions.

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دور التصوير بالرنين المغناطيسى الديناميكى بالصبغة وتصوير معامل الانتشار فى وصف البؤر الكبدية عالية الدموية فى مرضى التليف الكبدى

هناك أنواع مختلفة من البؤر العالية الدموية التى تصيب الكبد المتليف، ولكن المشكلة الأساسية هى كيفية التفرقة بين البؤر الحميدة والسرطانية من أجل تقديم الرعاية اللازمة للمرضى المعرضين للبؤر ذات الخلايا الكبدية السرطانية. تعتمد متابعة مريض تليف الكبد على نتائج فحص الموجات فوق الصوتية للكشف عن البؤر الكبدية ثم التصوير ثلاثى المراحل بالأشعة المقطعية لتقييم نمط ديناميكا الدم الانتقالية للبؤر الكبدية خلال مختلف المراحل كمؤشر لمنبع التغذية الدموية للبؤر الكبدية مع تحليل دلالات الأورام. ولكن الأشعة المقطعية ودلالات الأورام لا يكفيان أحياناً فى تشخيص نوع البؤر ولاقى تحديد مكانها بدقة.

يعد التصوير بالرنين المغناطيسى التقليدى فى تقييم البؤر الكبدية على تقنيات ثلاث أساسية وهى وتقنية بالصبغة التقليدية الجادولينيوم وقياس معامل الانتشار كمياً ونوعاً من أهم التقنيات الحالية لتشخيص البؤر السرطانية. ويهدف هذا البحث لقياس مدى دقة نتائج هذا الفحص فى الكشف عن البؤر السرطانية. وقد توصل إلى أن توفر تقنيات التصوير بالرنين المغناطيسى التقليدية جنباً إلى جنب مع الرنين المغناطيسى الديناميكى بالصبغة وتصوير معامل الانتشار وقياسه تشخيصاً أكثر دقة للبؤر العالية الدموية التى تصيب الكبد المتليف. التقييم النوعى لتصوير معامل الانتشار وخرائط معامل الانتشار الظاهرى الخاصة بهم، فى حد ذاتها، لديهم د قة عا مة مماثلة، ويمكن استخد ا مه بدون تصوير الرنين المغناطيسى الدينا ميكى بالصبغة خاصة عندما يكون ممنوع أو غير متوفر. كانت قيم معامل الانتشار الظاهرى الكمية أقل دقة من التقييم النوعى لتصوير معا مل الانتشار. كلما زادت قيمة بى، كان الكشف عن البؤر الخبيثة الصغيرة أفضل، مع وجود نسب أقل من التشخيص السلبى الكاذب.