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# Determine Sensitivity of Diffusion Weighted Imaging for Diagnosis of Hepatocellular Carcinoma, Keeping the Liver Dynamic Post Contrast MRI as Gold Standard

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## Abstract

**Background:** Current guidelines establish hepatocellular carcinoma (HCC) diagnosis on imaging by presence of arterial phase enhancement with subsequent portal and/or delayed phases hypo enhancement/washout, defining this as hall mark for HCC radiological diagnosis. This typical vascular pattern has limits, where the lesion is hypo vascular or smaller than 1 cm diameter. Many papers have been published that focuses on diffusion weighted imaging (DWI), yet to the best of our knowledge no consistent data is yet available that accurately establishes the diagnostic accuracy of DWI in HCC. DWI acts as adjuvant sequence. Our paper focuses on determining the accuracy of DWI in HCC diagnosis, adding as a milestone in incorporating this in international guidelines as standalone sequence.

**Purpose:** To evaluate whether or not DWI sequence can accurately detect hepatocellular carcinoma (HCC).

**Method and Materials:** In this retrospective study, we enrolled 104 diagnosed HCC cases from hospital database from July 2018 to October 2020 after IRB approval. Those 104 HCCs underwent MR-imaging at 1.5 tesla. MR acquisition comprised unenhanced T1- and T2-weighted images and post-contrast gadolinium enhanced T1weighted image after 25, 60, 180 second (dynamic phase) gadolinium-DTPA. DWI was performed by SSEPI sequence. Data analysis was done using SPSS version 21 and results were complied.

**Results:** The sensitivity of DWI MRI sequence for detecting HCC was found out to be 82.2%, specificity 87.5%, positive predictive value 98.7%, negative predictive value 29.1% and diagnostic accuracy 82.6% thus can be used as a reasonable alternative to dynamic MRI in cases when contrast injection is contraindicated.

**Conclusion:** Our study showed restricted diffusion on DWI images can be used as a reasonable alternative imaging sequence for diagnosing HCCs specially in cases when dynamic MRI imaging cannot be performed.

**Keywords:** Hepatocellular carcinoma; DWI; Diagnostic Non-invasive; Hypo vascular; HCC

**Abbreviations:** FNH: Focal Nodular Hyperplasia; ADC: Apparent Diffusion Coefficient; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; LIRADS: Liver Imaging Reporting Data System; USG: Ultrasonography; NAFLD: Non-Alcoholic Fatty Liver Disease; HCC: Hepatocellular Carcinoma; DWI: Diffusion Weighted Imaging

## Introduction

There is increasing incidence of hepatocellular carcinoma (HCC) worldwide, being the fifth commonest cancer and holds being the second commonest reason of cancer death [1]. It is alarmingly on rise in Pakistan [2,3]. Multiple risk factors for HCC have been documented worldwide, a few include alcohol, hepatitis C and hepatitis B infection and non-alcoholic fatty liver disease (NAFLD). With current disease load it is crucial to accurately diagnose HCC at the early stage for reducing the morbidity and mortality. The rate limiting step in the disease burden is early diagnosis [4]. Non-invasive imaging modalities have a fundamental part in the diagnosis of HCC. Ultrasonography (USG) remains the baseline imagining modality. It is extensively used as its screening test. The documented sensitivity of HCC diagnosis through USG is 51%-87% and specificity of 80%-100% [5]. Followed by conclusive enhancement pattern on dynamic computed tomography scan of liver (CT)or/and magnetic resonance imaging (MRI) liver dynamic as described in Liver Imaging Reporting Data system

(LIRADS). This consists of arterial phase enhancement followed by washout on portal venous and/or delayed phases. This does not requirement histopathological confirmation [6,7]. In addition to these, promising results are acquired from DWI in adjunct to hepatobiliary contrast study on MRI side by side perfusion imaging and elastography. Such modalities have an important role in surveillance, staging and prognosis of disease, as well as early detection and characterization [8].

Several studies about diagnosis of HCC have reported high sensitivity of diffusion weighted imaging combined with dynamic contrast enhanced magnetic resonance imaging. Yet to best of our literature review only limited studies are available that compares the DWI efficacy alone in diagnosis of HCC against post-contrast dynamic MRI. We therefore hypothesize, on the basis of our clinical experience, that DWI may act as a standalone tool for recognizing HCC lesion in a patient with established cirrhotic liver morphology. The aim of our study is to evaluate the diagnostic accuracy of DWI in detecting HCC keeping dynamic contrast enhanced T1WI as gold standard.

## Material and Methods

This retrospective study was performed followed approval from Institutional Ethic committee of medical education and research. All patients with known cirrhotic liver morphology due to hepatitis B or C virus were included in the study. The included lesions according to LIRADS classification were all LIRADS 4 (probably HCC) and LIRADS 5 (definitely HCC) lesions. Whereas any patient with post treated status either through transcatheter arterial chemoembolization or radiofrequency ablation for HCC were excluded. This resulted in total 104 patients with confirmed diagnosis of HCC from electronic data base of hospital from July 2018 to October 2020. Fully written informed consents were received and signed from all included patients at the time of history taking in outdoor patient department. At the time of presentation, it was ensured that each patient did not have had any previous loco-regional therapy.

MRI were performed using 1.5 Tesla Titan Toshiba machine. Examination included non-enhanced T1 and T2 weighted axial and coronal views (out of phase and in-phase images) and axial SPIR weighted sequence and diffusion weighted images of MRI. Post-contrast T1 weighted MRI axial dynamic images were acquired after a bolus of injection of 0.1mmol/kg body weight of the gadolinium-DTPA at the rate of 2ml/sec, which is flushed using 20ml of sterile normal saline solution through a power injector. Axial T1 post-contrast images were acquired in triphasic manner; included one non-enhanced series then four consecutive post-contrast series consisting early arterial phase, portal phase, and delayed/hepatobiliary phases.

Data was analyzed by two separate radiologists. For the analysis of data, size was measured in longest axial dimension of lesion in hepatobiliary phase of dynamic postcontrast T1 sequence. Intensity pattern of signal on T1, T2 and fat suppressed sequences were documented. Lesion enhancement pattern and presence of washout on subsequent sequences was evaluated on postcontrast dynamic MRI. Similarly, the index lesion was interpreted on DWI and apparent diffusion coefficient sequences (ADC).

Lesions having high signal intensities than background liver on DWI and low signals on ADC map were considered true positives for HCC showing restricted diffusion. Those lesions showing typical enhancement pattern on dynamic postcontrast MRI showing no restricted diffusion were considered as false negatives while false positive were lesion with restricted diffusion in absence of typical lesion enhancement. Lesions with no arterial phase enhancement and no restricted diffusion were considered true negatives.

Data was analyzed using version 25 of SPSS. The continuous variables were presented as mean with standard deviation while categorical data was displayed as frequency percentages. A 2 x 2 contingency table was constituted calculating sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy of DWI in detecting HCC while dynamic postcontrast imaging with arterial phase enhancement and washout was considered as gold standard.

## Results

There were 104 patients, among them 86.5% (90) were males whereas, 13.4% [14] were females. Their age was ranging 39-78 years (mean age of 55.8 years ± 9.82). Among our total 104 lesions; size of the lesion was variable. 20 (19.2%) lesions had size between 1-2 cm, 39 (37.5%) lesions had sizes between 2-5cm and 45 (43.3%) lesions had sizes more than 5cm (Table 1).

**Table 1**: Size of the lesion (cm).

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | | 20 | 19.2 | 19.2 | 19.2 |
| | | 39 | 37.5 | 37.5 | 56.7 |
| | more than 5 | 45 | 43.3 | 43.3 | 100 |
| | Total | 104 | 100 | 100 | |



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Interpretation of lesion on post-contrast MRI showing arterial phase enhancement on post-T1WI followed by washout on venous and delayed phases turned out to be 92.3% (96 lesions) characterized as LR-5 lesions; while 8 (7.6%) lesions showed no enhancement on arterial phase however washout in the lesion was present on delayed phase images characterized as LR-4 lesions. These lesions were then interpreted on DWI sequence as well. Out of total 104 lesions, 79 lesions were showing homogenous bright signal on DWI making it about 91.1%. These lesions were similarly low on ADC representing true positives (Figure 1). 7 out of 104 lesions turned out to be true negatives as no restricted diffusion was seen in the lesions which lacked typical HCC enhancement pattern. 1 lesion turned out to be false positive on DWI while 17 out of 104 lesions were false negatives as no diffusion signal abnormality was detected even in the presence of typical HCC pattern enhancement. The sensitivity of DWI MRI sequence for detecting HCC was found out to be 82.2%, specificity 87.5%, positive predictive value 98.7%, negative predictive value 29.1% and diagnostic accuracy 82.6%.

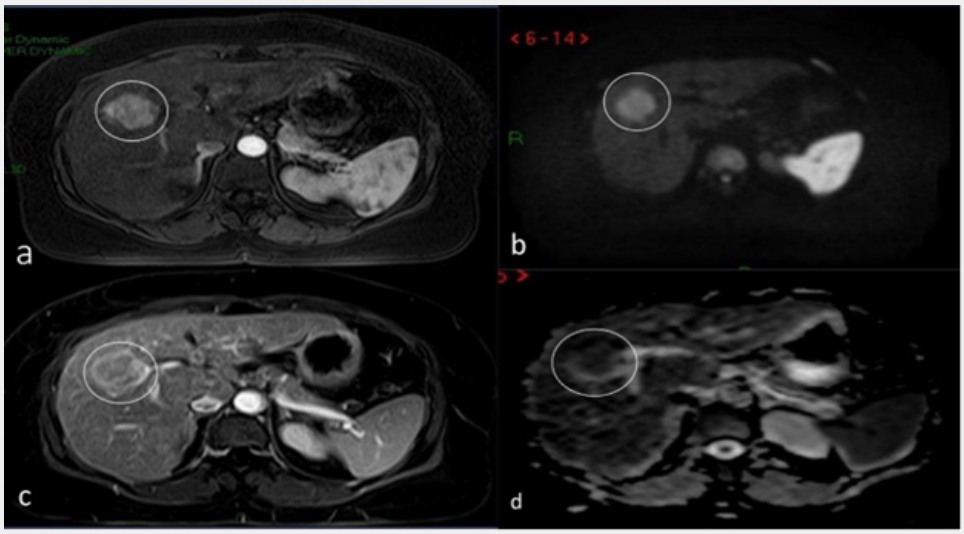


**Figure 1:** (a) Axial arterial and (c) axial venous phase MRI of liver depicting right lobe lesion showing typical enhancement on arterial phase and washout on venous phase MRI. (b) DWI shows restricted diffusion appearing low on ADC sequence (d) in similar lesion.

## Discussion

HCC remains one of the most common cancers worldwide and is second most common cause of cancer associated mortality [1,2]. In order to avail the curative treatment; early diagnosis is crucial as they are aggressive tumors with massive metastasis [9]. Early diagnosis with no metastatic spread makes the patient eligible for treatment which offers a good prognosis ranging between 50-70% 5-year survivals [10]. HCC can be diagnosed using non-invasive radiological imaging criteria that is used as a gold standard. This includes arterial phase enhancement followed by washout on portal venous and/or delayed phases on dynamic contrast enhanced MRI or CT [10,11].

This criterion has limitation in patients where performing a contrast enhanced imaging study is not feasible either due to chronic kidney failure, where contrast cannot be used due to risk of renal injury or potential nephrogenic systemic fibrosis or in those with cases where patients have documented allergy to contrast material. Such cases call for an additional sequence which does not use contrast and yet provides definitive results. DWI sequence is progressively used in characterization and detections of liver lesion. This benefit it attributed to echo-planar along with parallel imaging techniques. This characteristic has improved image quality with decrease of several artefacts resulting from bowel peristalsis, breathing and cardiac motion [12]. There are several studies that have reported the significant sensitivity of DWI when used in combination with dynamic contrast enhanced MRI in diagnosing HCC. To the top of our awareness and understanding only limited studies are available that compares the efficacy of DWI against contrast enhanced dynamic MRI.

We performed our study for the assessment of DWI as a standalone sequence for evaluation and diagnosis of HCC, taking post-contrast dynamic MRI as gold standard. Owing to immense soft tissue resolution and lack of ionizing radiation MRI is playing a crucial role. According to N Bharwani et al. [13] DWI is widely used as a standard imaging sequence with the usual non-contrast T1/T2 weighted imaging and post-contrast T1 dynamic for evaluation of liver. This is what was introduced in our hospital in 2019 and played a milestone for HCC diagnosis. In past a study performed by Nasu et al. [14] on 125 surgically resected hyper vascular HCCs, which were depicting hyperintense signal in lesions on DWI, the sensitivity of DWI in detecting HCCs was 80.6% which is comparable to sensitivity in our study which is 82.2%. A study performed by Piana G et al. [15] on 91 patients


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that documented that combination of DWI with the conventional post-contrast MRI enhanced the detection of HCC in comparison to post-contrast alone showing similar results to our study. In similar study, these results were stable in hepatic lesions for size smaller than 2cm. In this study, 91.1% of HCCs were hyperintense on DWI. This percentage is slightly greater than in earlier studies as stated before in Piana et al. where 82% or 72% of HCC were hyperintense, whereas about 91.2% of arterialized HCC were hyperintense in the study by Nasu et al. [14,15]. Through our study, a higher sensitivity of DWI alone was also detected compared a study by Le Moigne F et al. [16].

In a more recent data analysis of nine studies, showing nearly similar results to ours where sensitivity of DWI was 81% and specificity of 89%. However, contrary to our study this paper documented that DWI in combination with contrast enhanced MRI had a higher sensitivity than that of the DWI alone [17]. These studies supported the combination of DWI with CE-DWI and had certain reservation on DWI alone in detecting HCC. There are certain studies that mentioned the difficulty in differentiating liver carcinoma from additional firm liver masses like focal nodular hyperplasia, metastasis or adenomas. Preceding studies have cited as well that on DWI sequence alone it may be difficult to differentiate HCC from other solid hepatic lesions like focal nodular hyperplasia (FNH), adenomas, and metastasis. In a recent paper by Nowicki TK [18], described that solid hepatic lesions show ADC value that overlaps with that of HCC. However, the primary study population of our research are patients with either known or high suspicion of HCC with background cirrhotic liver morphology. With such liver morphology possibility of FNH and adenomas is least [19]. DWI may be helpful and non-invasive substitute for the diagnosis of HCC in patients with impaired renal function or contrast allergies stopping the use of contrast [20]. As presented in this paper, DWI can act as good diagnostic tool in the evaluation of HCC regardless of size.

Limitations of study included retrospective study performed at a single centre. Histopathological confirmation was not among inclusion/exclusion criteria as HCC can be confidently diagnosed on imaging and does not always require histopathological confirmation. Further larger studies are still needed to establish the value of DWI alone for detecting HCC.

## Conclusion

Our study showed restricted diffusion on DWI images can be used as a reasonable alternative imaging sequence for diagnosing HCCs specially in cases when dynamic MRI imaging cannot be performed. Determining novel non-invasive diagnostic modality to add value and improvement in diagnosis of HCC is challenging, this study will open doors for innovative research in future.

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