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Beyond the vascular profile: conventional DWI, IVIM and kurtosis in the assessment of hepatocellular carcinoma

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Abstract. – OBJECTIVE: To describe the role of the Diffusion Weighted Imaging (DWI) in the assessment of hepatocellular carcinoma (HCC).

MATERIALS AND METHODS: Several electronic databases were evaluated in the present review. The search included articles published from January 2010 to May 2019. The references of all articles were also evaluated. All titles and abstracts were assessed, and only the studies of DWI in patients with HCC were retained.

RESULTS: HCC is the most common primitive hepatic cancer. The non-invasive radiological criteria for HCC diagnosis are based on the presence of the specific vascular profile characterized by contrast uptake during arterial phase, defined as arterial hyperenhancement, followed by washout in the venous/portal phase. However, arterial hyperenhancement and wash out appearance have a sensitivity rate of 50-60% in lesion smaller than 2 cm. Therefore, other functional parameters have been introduced in the detection and characterization of HCC nodules. DWI has been applied to liver imaging as an excellent tool for detection and characterization of focal liver lesions, increasing clinical confidence and decreasing false positives. The assessment of DW images can be done qualitatively and quantitatively, through the apparent diffusion coefficient (ADC) map. Intravoxel incoherent motion (IVIM) is a more sophisticated analysis, a biexponential model, to better defining the relationship between signal attenuation and increasing b value that separately reproduces tissue diffusivity and tissue perfusion. Traditionally DWI approach to analyze data is founded on the hypothesis that water molecules diffuse within a voxel following a single direction with a Gaussian behavior without any restriction. However, according to the presence of microstructures, water molecules within biologic tissues exhibits a non-Gaussian phenomena proposed by Jensen in 2005 called Diffusion Kurtosis Imaging (DKI). This approach assesses the kurtosis coefficient (K) that shows the deviance of diffusion from a Gaussian approach, and the diffusion coefficient (D) with the correction of non-Gaussian bias. DKI is an advanced DWI model that quantifies non-Gaussian behavior of diffusion and provides both a corrected ADC, as well as the excess kurtosis of tissue, a measure of the extent to which tissue diffusion deviates from a Gaussian pattern. It is believed that the DKI model is more sensitive to tissue microstructural complexity than standard DW.

CONCLUSIONS: DWI should be an integral part of study protocol for HCC patients, considering the great advantages due to DWI and DWI-based approaches in detection and characterization of HCC.

Key Words:
HCC, DWI, ADC, IVIM, Kurtosis.

Introduction

Hepatocellular carcinoma (HCC) is the most common primitive hepatic cancer[1]. Patients who are diagnosed at an early stage without metastasis are eligible for curative therapies, and hence, have a good prognosis in the range of 50-70% survival rate at 5-year. However, the prognosis is poor when HCC is diagnosed at an advanced stage[1]. Therefore, an early detection of HCC and an accurate characterization of focal liver nodule on patient at risk for HCC is mandatory for a suitable patients management[2-5].

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The non-invasive radiological criteria for HCC diagnosis are based on the presence of the specific vascular profile characterized by contrast uptake during arterial phase, defined as arterial hyperenhancement, followed by washout in the venous/portal phase[3]. The typical vascular profile is due to hemodynamic changes in nodule during hepatocarcinogenesis[6]. However, arterial hyperenhancement and wash out appearance have a sensitivity rate of 50-60% in lesion smaller than 2 cm[6]. This is combined with the possibility that a hepatic nodule is detected during different steps of hepatocarcinogenesis or that the nodule shows a poorly histological differentiation. Therefore, other functional parameters have been introduced in the detection and characterization of HCC nodules[7]. Diffusion Weighted Imaging (DWI) has been applied to liver imaging as an excellent tool for detection and characterization of focal liver lesions, increasing clinical confidence and decreasing false positives[2].

Materials and Methods

Search Criteria

Several electronic databases were used for the literature search: Scopus (Elsevier, http://www.scopus.com/), PubMed (US National Library of Medicine, http://www.ncbi.nlm.nih.gov/pubmed), Web of Science (Thomson Reuters, http://apps.webofknowledge.com/), and Google Scholar (https://scholar.google.it/). We used the following search terms: "HCC" AND "diffusion imaging" AND "detection" AND "characterization"; "HCC" AND "intravoxel incoherent motion" AND "detection" AND "characterization"; "HCC" AND "diffusion kurtosis imaging" AND "detection" AND "characterization". The search included articles published from January 2000 to May 2019. Moreover, the reference lists of the identified articles were evaluated. All titles and abstracts were examined, and only the studies on DWI in patients with HCC were retained. The exclusion criteria were inaccessibility of the full text, overview articles, and articles with topics other than DWI in HCC patients.

Discussion

Technical Features

DWI analyses water molecules movement due to their thermal energy (Brownian motion) as a physical property. So, DWI signal permits to evaluate indirectly tissue biological features. The Diffusion is physiological correlated to integrity of cell membranes, fibroses and macromolecules. Therefore, high cellularity, abscess, fibrosis or cytotoxic edema lead to diffusion restriction whereas low cellularity and necrosis lead to an unrestricted diffusion[6,8]. Eco Planar Imaging sequences are used for DWI, which are T2-weighted (W) sequences, acquired with single shot technique and Fat Saturation (FS). Several series of DWI are acquired through modification of the gradient strength and magnitude, defined as *b*-value. One series is obtained with a *b*-value of 0, meaning no gradient is applied and consequently no diffusion data are obtained, giving similar data by T2-W FS sequences. Another series should be obtained with a low *b*-value ($b < 100$), for lesion detection, whereas series obtained with a high *b*-value (such as $b = 800$ or more) are used for lesion characterization[6].The assessment of DW images can be qualitatively and/or quantitatively, with the apparent diffusion coefficient (ADC) map. ADC values are calculated for each voxel[6]. The ADC map is the graphical demonstration of the ratio of DW signal and its measurements may distinguish between benign and malignant tissues, thus allowing the characterization: low ADC values mean restricted diffusion, high ADC values mean free or unimpeded diffusion. As a non-invasive tool, DWI allows to draw conclusions about cellularity. However, the ADC values are related to the sequence acquisition protocol and suffer from a lack of reproducibility, especially in respiratory triggering techniques[3,6]. Accurate evaluation of ADC can be improved by acquiring a large number of *b*-values. Several authors assessed ADC as a tool for lesion characterization. The ADC values for HCC vary in literature widely between 0.94 and 2.87 and show a significant overlap between ADC values of metastases and even benign hepatocellular lesions[9-12]. Lesion characterization should therefore always be done in a combination with unenhanced and dynamic MRI data. Crucial disadvantages of DWI are given due to the low signal-to noise ratio, low spatial resolution and the susceptibility for artifacts (especially by motion and air-tissue interface, e.g., the liver subdiaphragm parts)[6].

Le Bihan et al[13,14] first described the intravoxel incoherent motion (IVIM) and evaluated a more sophisticated method, a biexponential model, to define the relationship between signal decrease and increasing *b* value that separately

reproduce tissue diffusivity and tissue perfusion. By using IVIM model and multiple, sufficiently low *b* values (< 200 mm^2/sec), not only can pure diffusion characteristics (*D*) be separated from pseudodiffusion caused by microscopic circulation in tissue, but perfusion characteristics (pseudodiffusion coefficient [*D**]) and their proportion (perfusion fraction [*f*]) can also be extracted[13,14]. The *D** and *f* values are the perfusion parameters, which could be used to analyze the vascularity of the tissue. According to the IVIM model, *D** is defined as the average blood velocity and the mean capillary segment length, and *f* measures the fractional blood volume of the microcirculation. Therefore, IVIM data can be evaluated either quantitatively or qualitatively; quantitative data may be useful for tissue characterization and functional assessment, while qualitative evaluation may be useful to identify disease. IVIM data enable improved detection and characterization of HCC[3].

Traditionally DWI approach to analyze data is founded on the hypothesis that water molecules diffuse within a voxel following a single direction with a Gaussian behavior without any restriction [4]. However, according to the presence of microstructures, water molecules within biologic tissues exhibits a non-Gaussian phenomena proposed by Jensen called Diffusion Kurtosis Imaging (DKI)[15]. This approach assesses the kurtosis coefficient (*K*) that shows the deviance of diffusion from a Gaussian approach, and the diffusion coefficient (*D*) with the correction of non-Gaussian bias.

DKI is an advanced DWI model that quantifies non-Gaussian behavior of diffusion and provides both a corrected ADC, as well as the excess kurtosis of tissue, a measure of the extent to which tissue diffusion deviates from a Gaussian pattern[15]. It is believed that the DKI model is more sensitive to tissue microstructural complexity than standard DWI. Several researches[16-23] have shown that DKI is more accurate than traditional ADC in tumor assessment.

Conventional DWI and Kurtosis in the HCC Characterization

The role of DWI and functional parameters obtained by DWI in HCC patient has been evaluated by different studies[24-30]. Lee et al[24] showed that the addition of DWI to the standard protocol with gadoxetic acid could allow to identify HCCs and dysplastic nodules. They showed that 86 HCCs (84.3%) showed hyperintensity on DWI; conversely, only 3 dysplastic nodules had this feature. Piana et al [25] showed that restricted diffusion and hyper-enhancement during arterial phase were more sensitive than conventional vascular criteria. DWI could be used as a helpful tool for HCC in patients with chronic liver disease, since it can accurately detect HCC in patients with chronic liver disease regardless of the lesion size[26]. However, several studies[31-34] have shown that DWI not allow to differentiate HCC from other hepatic lesions, since these solid lesions also have increased cellularity, showing ADC values that overlap with ADC values of HCC. The major limits of DWI are the different parameters used in DWI sequences which may affect the results of ADC. The different *b* values, selection method, bias of patient selection, pathological characteristic of lesions and measurement of ADC values may be reduced the reproducibility of the data[3].

Although ADC is a helpful tool for the diagnosis of tumor, the calculation of ADC by using a mono-exponential model does not account for the non-Gaussian diffusion behavior of water molecules in tissues. For this reason, more sophisticated non mono-exponential models, the kurtosis model, the stretched exponential model, and the statistical model, were proposed to evaluate complex water molecular motions. These non mono-exponential models can give more diffusion-related data and provide complementary parameters on the properties and features of tumor (Figure 1). Recently, non-Gaussian diffusion behavior has been described in HCC and several authors have also evaluated the utility of the non mono-exponential models for the characterization and the assessment of treatment response in HCC patients[35-39]. However, the knowledge is still limited on which non mono-exponential model could more accurately evaluate the non-Gaussian DW signal. Also, the reliability and repeatability of the fitted parameters of the non mono-exponential models have not been evaluated in terms of HCC. It is known that more complex models with more free parameters tend to overfit data, resulting in poor repeatability and limited use in clinical practice. Additionally, in order to capture the non-Gaussian diffusion behavior of water molecules in biological tissues, *b*-values larger than those employed in DWI are required. For the liver, maximum *b*-values of about 2000 s/mm^2 was proposed in previous studies. A higher *b*-value means a lower signal-to-noise ratio (SNR) and a poorer repeatability of the calcu-

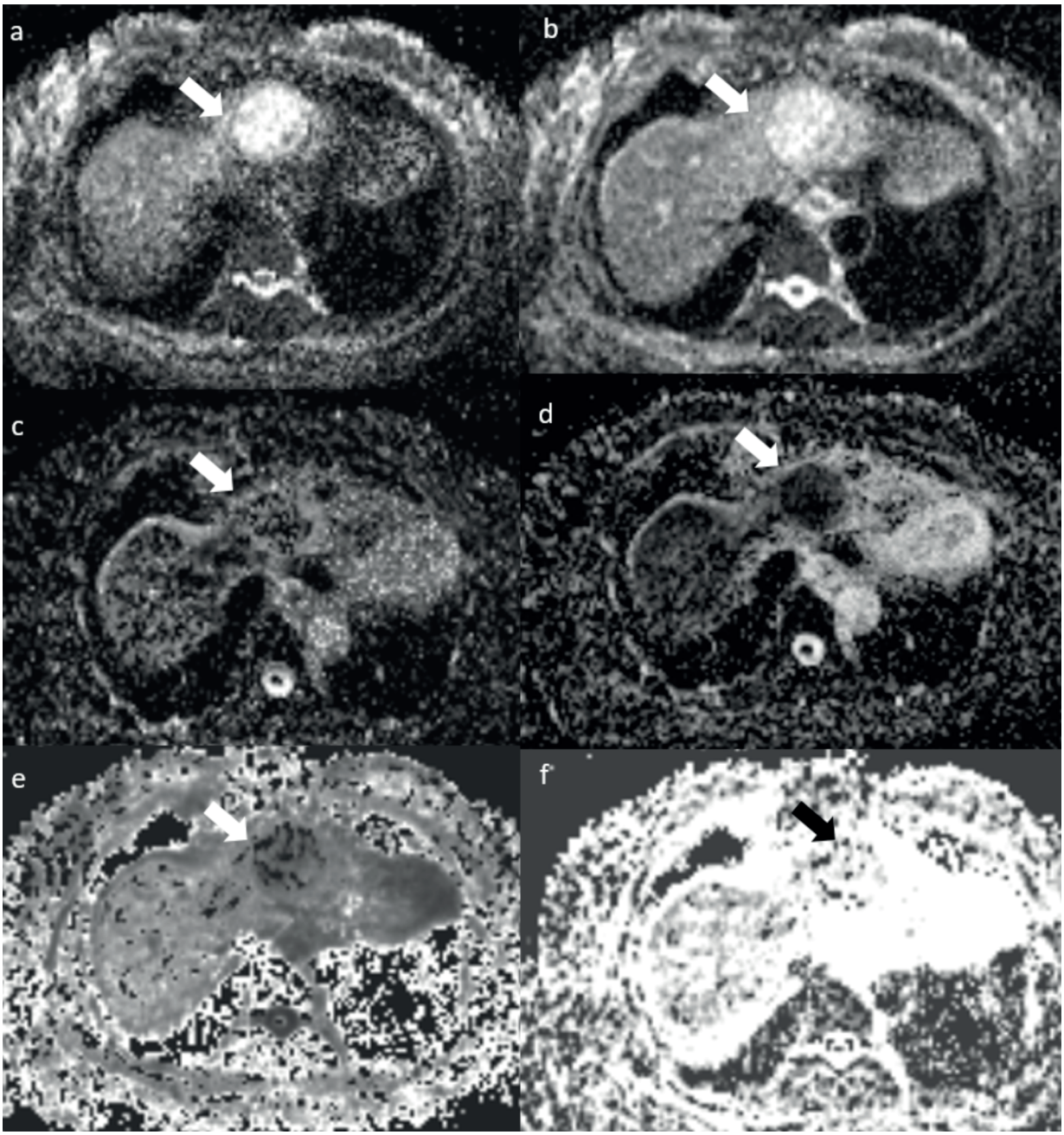

Figure 1. Woman 73 y with HCC on II hepatic segment. In **(a)** the apparent diffusion coefficient (ADC) map, in **(b)** pure tissue diffusion coefficient (Dt) map, in **(c)** pseudodiffusion coefficient (Dp) map, in **(d)** perfusion fraction (fp) map, in **(e)** mean apparent kurtosis coefficient (MK), **(f)** mean diffusion coefficient (MD).

lated parameters. Therefore, it is necessary to explore whether or not the non mono-exponential models can provide desirable repeatability of measurements for HCC[35]. Kuai et al[35] evaluated 3 different non mono-exponential models (kurtosis, stretched exponential, and statistical) in terms of fitting quality and repeatability of the fitted data, showing that the stretched exponential model provided the best fit to HCC, whereas the statistical model produced the largest fitting residuals. The repeatability of *K* from the kurtosis model was excellent, while the distributed diffusion coefficient (DDC) from the stretched model was just acceptable. The repeatability was good for other diffusion-related parameters. So, considering the model fit and repeatability, the

kurtosis and stretched exponential models are the preferred models for the description of the DW signals of HCC respect to the statistical model[35].

Rosenkrantz et al[36] performed *ex vivo* evaluation of DKI for assessment of HCC, using fresh liver explants. Twelve liver explants underwent MR study using a DKI sequence with maximal *b*-value of 2000 s/mm^2. A standard mono-exponential fit was used to calculate ADC, and a non-Gaussian kurtosis fit was used to calculate *K*, a measure of excess kurtosis of diffusion, and *D*, a corrected diffusion coefficient accounting for this non-Gaussian behavior. The mean value of these parameters was measured for 16 HCCs based upon histologic findings. For each metric, HCC-to-liver contrast was calculated, and coefficient of variation (CV) was computed for voxels within the lesion as an indicator of heterogeneity[36]. They showed that the 16 HCCs demonstrated intermediate-to-substantial excess diffusional kurtosis, and mean corrected diffusion coefficient D was 23% greater than mean ADC. HCC-to-liver contrast and CV of HCC were greater for *K* than ADC or *D*, although these differences were significant only for CV of HCCs. ADC, *D*, and *K* showed significant differences between non-, partially and completely necrotic HCCs. Among seven non necrotic HCCs, cellularity showed a strong inverse correlation with ADC, a weaker inverse correlation with *D*, and with a direct correlation with *K*[36]. Goshima et al[37] assessed DKI and conventional DWI for evaluating treatment response in hypervascular HCC. Sixty-two patients (112 HCCs; viable, n = 63; non-viable, n = 49); underwent MRI; DKI was performed with different *b* values: 0, 100, 500, 1000, 1500, and 2000 s/mm^2. The mean kurtosis (*MK*) and ADC values of the hepatic parenchyma and of the HCCs were analyzed. The detectability of viable HCC based on *MK* and ADC parameters was compared. They also evaluated the correlation between Child-Pugh classes and *MK* or ADC values[37]. The *MK* value was significantly higher for the viable group than for the non-viable group. The mean ADC value was significantly lower for the viable group than for the non-viable group. The sensitivity, specificity, and AUC of the ROC curve for the assessment of HCC viability were greater using *MK* than using ADC[37]. Considering that viable HCCs are characterized by structural complexity, with higher cellularity with nuclear atypia, more vascular hyperplasia or necrosis, and occasionally fatty deposition, it is known that DKI model represents better the complexity of biological tissues. However, it is essential that DKI might be evaluated in a reproducible manner and therefore is mandatory to standardize the protocol, establishing the strength and number of "*b*" values, the kinetic model application and the analysis methodology to calculate derivate quantitative parameters.

Prognostic Features: Role of Conventional DWI, IVIM and Kurtosis

The pathological grade of HCC is deeply connected to the prognosis, and it is one of the independent predictive features for recurrence and long-term survival after hepatic resection[38,40]. However, it is challenging to define accurate preoperative grade using imaging modalities.

Several studies[40-44] have assessed the association between quantitative parameters by DWI and histological grade of HCC. Chen et al[42], in a meta-analysis, found that for distinguishing well differentiated nodules from higher grades, DWI showed a low sensitivity (54%), high specificity (90%), and an excellent diagnostic performance. Conversely, in differentiating poorly differentiated nodules from lower grades, the sensitivity was 84%, the specificity 48%, showing a moderately high diagnostic performance[42]. Granata et al[3] found that DWI could be used to predict the histological grade of HCC; in fact, they showed that there was a good correlation between ADC and grading, between perfusion fraction (*fp*) and grading, and between tissue pure diffusivity (*Dt*) and grading. Nakanishi et al[41] showed not only the utility of DWI in the assessment of grading, but also the possibility to use ADC as a preoperative biomarker of early recurrence. However, while some investigators have reported that the histologic differentiation of HCC showed an inverse correlation with ADC values[43,45], another has reported that there was no relationship[41]. These conflicting results regarding ADC measurements can be attributed to two main factors: the variable strength and number of *b* values used for DWI in each study and the "pseudo-diffusion" effect generated by active non-Brownian water motion processes, such as blood flow, which contribute to apparent diffusion. The mayor limit of DWI and IVIM parameters, as suggested by Ichikawa et al[46], is related to the fitting approaches used to obtained quantitative parameters, thus the fitting would be robust even though some errors might have occurred during image acquisition[46].

Microvascular invasion (MVI), defined as microscopically detected tumor thrombi within

small tumor or peritumoral vessels, to day, is considered a major risk factor of recurrence and survival in HCC patients after resection (LR)[47]. Also, macrovascular invasion and MIV have been shown to increase the risk of recurrence after liver transplantation (LT)[48-50]. Conversely, for patients referred for LR, the rule of MVI is not widely accepted. In fact, there is not well-defined relationship between overall (OS) and disease-free survival (DFS) with MVI[50]. Nevertheless, the evaluation of MVI could be significant in the choice of different treatment, as between LR or ablation therapies[51], or to identify a tailored post therapy follow-up[52]. Imaging techniques have been unsuccessful for the assessment of MVI since it is a microscopic data and the criteria for pre surgical diagnosis are not well established. DWI is an interesting tool in the assessment of MIV (Figure 2)[53-62]. In fact, as confirmed by Li et al[59] histogram analysis of IVIM based on whole

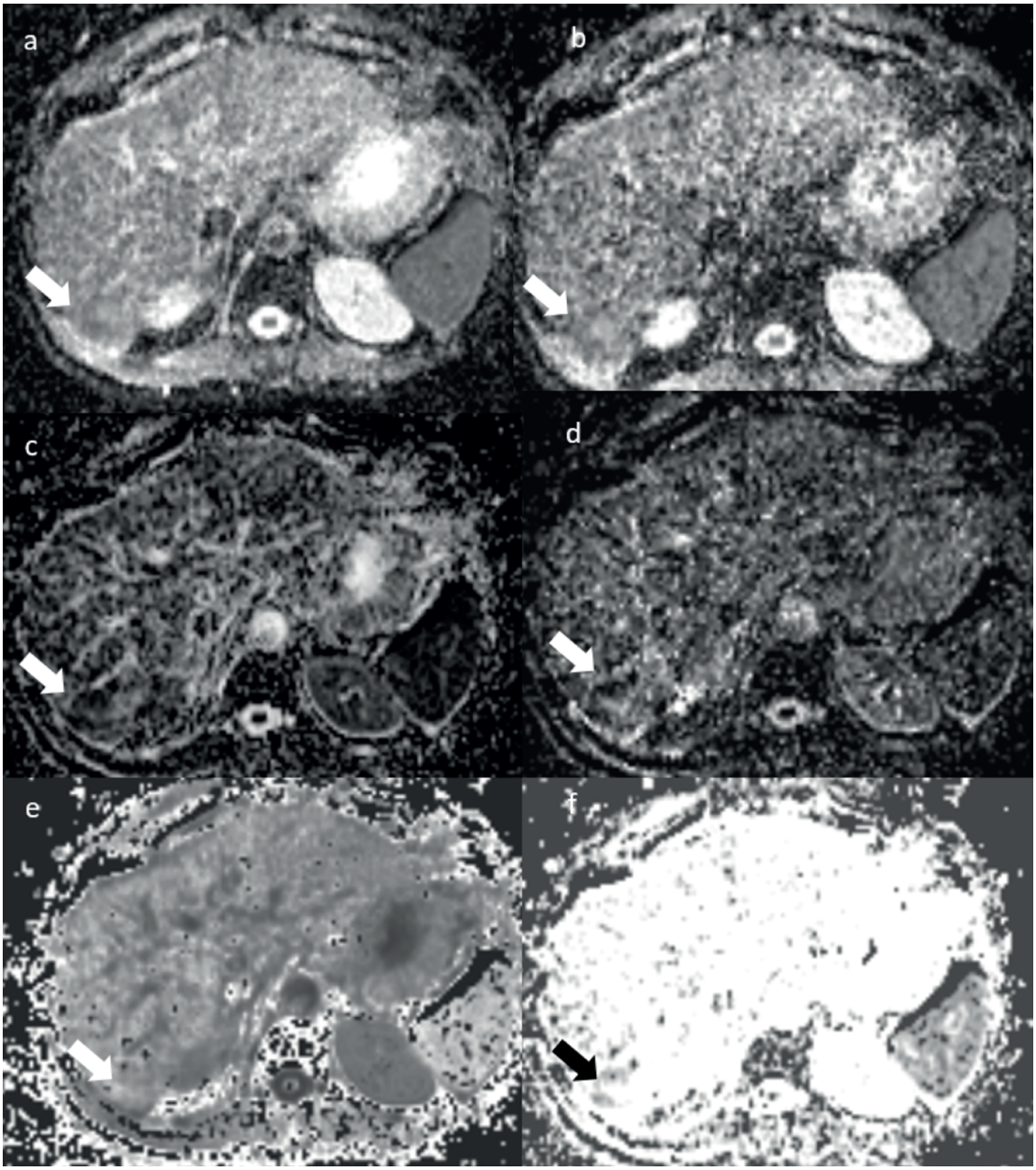

Figure 2. Man 67 y with HCC with MIV on VI hepatic segment. In **(a)** the apparent diffusion coefficient (ADC) map, in **(b)** pure tissue diffusion coefficient (Dt) map, in **(c)** pseudodiffusion coefficient (Dp) map, in **(d)** perfusion fraction (fp) map, in **(e)** mean apparent kurtosis coefficient (MK), **(f)** mean diffusion coefficient (MD).

tumor volume can be useful for predicting MVI. The 5th percentile of D was most useful value to predict MVI of HCC[59]. Also, Zhao et al[60] investigated the role of IVIM parameters in predicting MVI in HCC patients. They assessed ADC, *D*, *D** and *f* , relative enhancement (RE) and radiological morphological features. Univariate analysis revealed that HCCs with MVI had a higher portion of an irregular tumor shape than HCCs without MVI. ADC, *D* value was significantly lower in HCCs with MVI. Multivariate analysis showed that an irregular shape and *D* value ≤ 1.16×10-3mm^2/sec were independent predictors for MVI. Combining the two factors of an irregular shape and *D* value, a sensitivity of 94.4% and specificity of 63.6% for predicting MVI was obtained[54]. Wang et al[58] assessed the DKI and conventional MR imaging findings including ADC and morphologic features for prediction of MVI. They assessed 92 histopathologically confirmed HCCs (40 MVI-positive lesions and 52 MVI-negative lesions). Univariate and multivariate logistic regression analyses were used to evaluate the relative value of these parameters as potential predictors of MVI. They showed that features significantly related to MVI at univariate analysis were increased mean kurtosis value, decreased mean diffusivity value, ADC value, presence of infiltrative border with irregular shape and irregular circumferential enhancement. At multivariate analysis, mean kurtosis value, as well as irregular circumferential enhancement, were independent risk factors for MVI[58].

Conclusions

In conclusion, DWI should be an important part of the study protocol for HCC patients, considering the great benefits due to DWI and DWI-parameters in detection and characterization of HCC, and that now DWI has been included in the Liver Imaging Reporting and Data System. However, these methods show several limitations. First, the diagnostic efficacy of DWI to detect HCC could be degraded since there is not a standardized acquisition protocol, with particular regard to the purpose of optimal *b* values across different medical centers. Therefore, universal thresholds for ADC and other quantitative parameters may not be acquirable. Second, DWI is sensitive to motion artifact; thus, detection and characterization of lesions can be mostly affected in the presence of motion artifacts.

Conflict of Interest

The authors have no conflict of interest to be disclosed. The authors confirm that the article is not under consideration for publication elsewhere. Each author has participated sufficiently to take public responsibility for the manuscript content.

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