ORIGINAL ARTICLE

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Quantitative Evaluation of Hepatic Microstructural Changes in Hepatocellular Carcinoma Using Diffusion Tensor Imaging

Difüzyon Tensör Görüntüleme ile Hepatoselüler Karsinomda Hepatik Mikroyapısal Değişikliklerin Kantitatif Değerlendirilmesi

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ABSTRACT

Aim: Magnetic resonance imaging (MRI) is a fundamental imaging modality in the diagnosis, management, and follow-up of hepatocellular carcinoma (HCC). Diffusion-based imaging techniques have been shown to potentially play a significant role in the characterization of focal liver lesions. The aim of this study was to evaluate the contribution of diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) in the diagnosis of HCC by comparing DWI and DTI parameters with those of cirrhotic and non-pathological liver parenchyma.

Materials and Methods: This retrospective study included 62 patients with HCC, 56 with cirrhosis, and 52 with non-pathological liver parenchyma who underwent 1.5-T MRI. DWI and DTI sequences were acquired using b-values of 50-800 sec/mm^2 and 20 diffusion-encoding directions. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were calculated and compared across the groups.

Results: ADC values were significantly lower and FA values significantly higher in HCC compared to cirrhotic and non-pathological parenchyma ($p<0.05$). Mean FA was 0.46±0.14 for HCC, 0.39±0.08 for non-cancerous parenchyma, and 0.40±0.07 for both cirrhotic and non-pathological parenchyma. An FA cut-off of 0.45 yielded 38.7% sensitivity and 94.2% specificity [area under the curve (AUC): 0.653, 95% confidence interval (CI): 0.554-0.751] vs. non-pathological parenchyma, and 62.9% sensitivity and 75.0% specificity (AUC: 0.649, 95% CI: 0.542-0.745) vs. cirrhotic parenchyma.

Conclusion: FA values reflected moderate anisotropy in HCC, cirrhotic, and non-pathological liver parenchyma. Although FA differed significantly between HCC and non-malignant tissues, its modest sensitivity limits its utility as a stand-alone biomarker.

Keywords: Cirrhosis, diffusion tensor imaging, diffusion weighted imaging, hepatocellular carcinoma, liver, magnetic resonance imaging

ÖZ

Amaç: Manyetik rezonans görüntüleme (MRG), hepatosellüler karsinomun (HSK) tanı, yönetim ve takip süreçlerinde temel bir görüntüleme yöntemidir. Difüzyon temelli görüntüleme tekniklerinin fokal karaciğer lezyonlarının karakterizasyonunda tamamlayıcı bir rol oynayabileceği gösterilmiştir. Bu çalışmanın amacı, HSK tanısında difüzyon ağırlıklı görüntüleme (DAG) ve difüzyon tensör görüntüleme (DTG) parametrelerinin katkısını, sirotik ve normal karaciğer parankimi ile karşılaştırarak değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya, 1,5 T MRG yapılan 62 HSK hastası, 56 siroz hastası ve 52 normal karaciğer parankimi olan birey dâhil edildi. DAG ve DTG dizileri, 50-800 s/mm^2 b-değerleri ve 20 difüzyon kodlama yönü ile elde edildi. Fraksiyonel anizotropi (FA) ve görünen difüzyon katsayısı (ADC) değerleri hesaplanarak gruplar arasında karşılaştırıldı.

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Bulgular: HSK'da ADC değerleri anlamlı şekilde daha düşük, FA değerleri ise sirotik ve normal parankime kıyasla anlamlı şekilde daha yüksekti (p<0,05). Ortalama FA değeri HSK için 0,46±0,14, non-kanseröz parankim için 0,39±0,08, sirotik ve normal parankim için 0,40±0,07 idi. FA için 0,45 eşik değeri kullanıldığında, HSK'yı normal parankimden ayırt etmede duyarlılık %38,7, özgüllük %94,2 [eğri altındaki alan (AUC): 0,653, %95 güven aralığı (GA): 0,554-0,751); sirotik parankimden ayırt etmede ise duyarlılık %62,9, özgüllük %75,0 (AUC: 0,649, %95 GA: 0,542-0,745) olarak bulundu.

Sonuç: FA değerleri HSK, sirotik ve normal karaciğer parankiminde orta düzeyde anizotropiyi yansıtmaktadır. FA, HSK ile non-malign parankim arasındaki farkı yansıtmakla birlikte, sınırlı duyarlılığı nedeniyle tek başına tanısal biyobelirteç olarak kullanımı kısıtlıdır.

Anahtar Kelimeler: Difüzyon ağırlıklı görüntüleme, difüzyon tensör görüntüleme, hepatoselüler karsinom, karaciğer, manyetik rezonans görüntüleme, siroz

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related mortality worldwide, according to the latest GLOBOCAN data from the World Health Organization (https://gco.iarc.fr/). The age of onset for HCC varies depending on sex, geographic region, and associated risk factors[1]. Concomitant cirrhosis is found in 80% of cases of HCC[2]. Hepatitis B virus (HBV) is the most common cause of virus-associated HCC and is also the predominant etiology in cases without concomitant cirrhosis[3].

Diffusion tensor imaging (DTI) is widely used in neuroimaging, particularly for fiber tractography, but it has also been applied to the liver in a number of publications[4-17]. These studies have explored various aspects of liver DTI, including sequence optimization, hepatic isotropy, fibrosis assessment, and ischemia-reperfusion injury. However, only a few have focused on its use in the evaluation of focal liver lesions, and this area remains underexplored. Prior studies have predominantly evaluated apparent diffusion coefficient (ADC) values, while comprehensive analysis of diffusion tensor parameters particularly fractional anisotropy (FA) in HCC is still limited[4,5].

Although the liver parenchyma is generally considered isotropic, the anisotropic properties of hepatic tumors remain controversial[6,7]. FA, the most commonly utilized DTI-derived parameter in clinical practice, quantifies the degree of anisotropy. FA is a dimensionless value ranging from 0 to 1, where values closer to 1 indicate increasingly directional (anisotropic) diffusion[8].

The aim of this study was to compare DTI parameters of HCC with those of non-malignant liver parenchyma and present preliminary findings.

MATERIALS AND METHODS

Patients

This retrospective study included magnetic resonance imaging (MRI) examinations of 62 patients with HCC (13 females, 49 males; mean age: 65.08±8.19 years, range: 45-84), 56 patients with cirrhosis (19 females, 37 males; mean age: 58.69±11.43 years, range: 20-79), and 52 individuals with non-pathological liver parenchyma (19 females, 33 males; mean age: 59.75±15.78 years, range: 18-84). All imaging was performed at our institution between January and December 2019. In 22 patients (35.5%), HCC diagnosis was confirmed histopathologically. In the remaining 40 patients (64.5%), HCC diagnosis was established based on characteristic MRI findings according to the 2018 Liver Imaging Reporting and Data System (LI-RADS) criteria and multidisciplinary consensus. Among all patients, 49 (79%) were categorized as LI-RADS 5, 11 (17.7%) as LI-RADS 4, and one patient each (1.6%) as LI-RADS 3 and LI-RADS M. Among the 22 histopathologically confirmed HCC cases, 19 (86.4%) were classified as LI-RADS 5, 2 (9%) as LI-RADS 4, and 1 (4.5%) as LI-RADS 3. All final diagnoses were based either on histopathological confirmation or multidisciplinary consensus in accordance with established imaging criteria.

Ethical approval was obtained from the Trakya University Faculty of Medicine Scientific Research Ethics Committee (desicion no: 03/17, date: 03.02.2020).

MR Examination - Image Acquisition

MRI was performed using a 1.5T system (Aera, Siemens Medical Systems, Erlangen, Germany) with an 18-channel body matrix coil. Patients were positioned supine, head first, with arms at their sides. DTI sequences were acquired after T1- and T2-weighted imaging and before dynamic contrast-enhanced sequences. Imaging parameters for DTI were as follows: b-values = 50-800 s/mm^2, repetition time/echo time: 6300/69 ms, slice thickness: 6 mm, interslice gap: 1.2 mm, number of slices: 40, matrix size: 192 × 115, number of signal averages: 1, and 20 diffusion encoding directions. Breath-hold technique was used during acquisition.

Image Analysis-Calculation of DTI Parameters

All imaging data were processed on a dedicated workstation (Syngo.Via VB10B, Siemens). T2-weighted and contrast-enhanced images were used for anatomical reference. ADC maps were automatically generated by the system for each diffusion tensor dataset. Region of interest (ROI) placement

avoided major vascular and biliary structures and was limited to the posterior segment of the right hepatic lobe. For lesion measurements, circular ROIs of 2 cm^2 were used when feasible (Figure 1). In lesions where a 2 cm^2 ROI could not be placed, the largest possible ROI was selected. For large lesions, the average of three ROI measurements on the same slice was recorded. Lesions smaller than 1 cm were excluded due to limited spatial resolution. In patients with HCC, ROIs were placed to avoid cystic and necrotic areas, selecting the most appropriate solid portion of the lesion.

Statistical Analysis

Comparisons of DTI parameters between the HCC, cirrhotic, and non-pathological liver groups were performed using either the Student's t-test or the Mann-Whitney U test, based on the normality of data distribution. ROC curve analysis was conducted to determine optimal diagnostic cut-off values for distinguishing HCC, and corresponding sensitivity, specificity, positive predictive value, and negative predictive value were calculated. A p-value of less than 0.05 was considered statistically significant. Interobserver agreement for the HCC measurements was evaluated by calculating intraclass correlation coefficients (ICCs) between two radiologists, using a two-way random effects model with absolute agreement. ICCs were calculated separately for diffusion-weighted imaging (DWI) ADC, DTI ADC, and DTI FA values. All statistical analyses were conducted using SPSS software (Version 25, IBM Corp., Armonk, NY, USA).

RESULTS

HCC was more prevalent among the elderly and male patients, with a male-to-female ratio of 3.7. HBV was the most common etiological factor in both the HCC and cirrhotic groups, observed in 59.7% (n=37) and 53.6% (n=30) of cases, respectively.

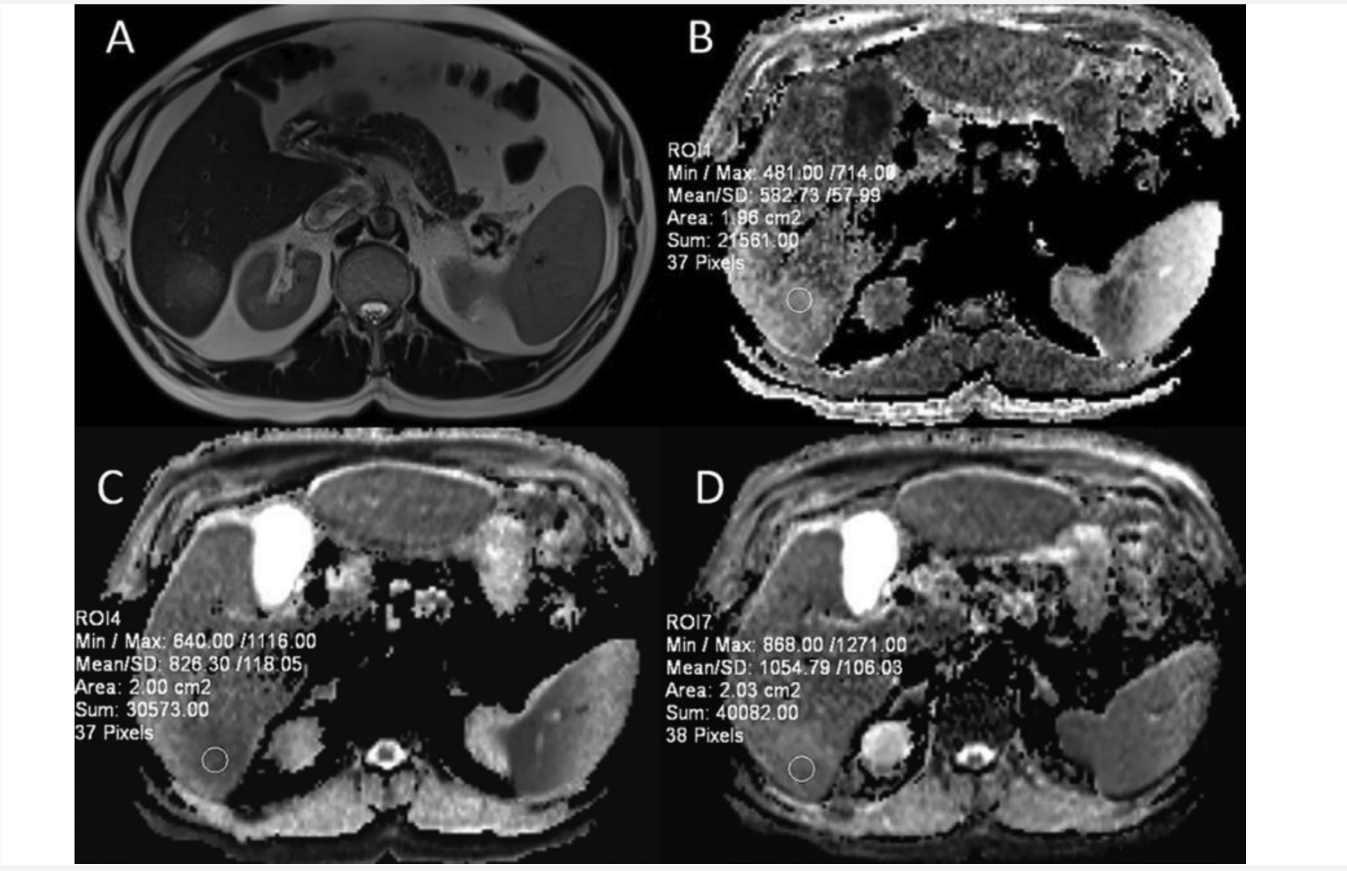

Figure 1. MRI images of a 60-year-old man with biopsy-proven hepatocellular carcinoma

T2-weighted images were used for anatomical orientation (A). Compared to surrounding liver parenchyma, hepatocellular carcinoma is seen as hyperintense (B) on the FA map (mean FA of 0.58) and hypointense on the ADC map (mean ADC of 0.83 x 10-3 mm^2/s) from diffusion tensor imaging data (C). On the ADC map from conventional diffusion imaging data (D), the mass is of intermediate signal intensity (mean ADC of 1.05 x 10-3 mm^2/s)

MRI: Magnetic resonance imaging, ADC: Apparent diffusion coefficient, FA: Fractional anisotropy, ROI: Region of interest, SD: Standard deviation

Patient Characteristics

Clinical and laboratory characteristics of all patient groups are summarized in Table 1.

MRI Features of HCC

In HCC patients, lesion characteristics were as follows: T1 hyperintensity in 37.1% (n=23), intermediate T2 hyperintensity in 82.3% (n=51), visually assessed diffusion restriction in 59.7% (n=37), arterial phase enhancement in 87.1% (n=54), capsular enhancement in the delayed phase in 85.5% (n=53), and washout in 88.7% (n=55). Satellite tumors were observed in 12.9% (n=8), lymphadenopathy in 25.8% (n=16), and vascular invasion in 27.4% (n=17). Intralesional fat was present in 11.3% (n=7), hemorrhage in 30.6% (n=19), and necrosis in 21% (n=13). The interobserver reliability analysis yielded ICC values of 0.858 [95% confidence interval (CI): 0.748-0.922] for DWI ADC, 0.853 (95% CI: 0.713-0.923) for DTI ADC, and 0.837 (95% CI: 0.712-0.910) for DTI FA, indicating good agreement between the two observers for the HCC measurements.

Conventional DWI Findings

Conventional DWI was performed in 45 out of 62 HCC patients. ADC values in HCC lesions were significantly lower than those in non-cancerous, cirrhotic, and non-pathological liver parenchyma. Using a cut-off ADC value of 0.99×10^{-3} mm^2/s to distinguish HCC from non-pathological parenchyma yielded a sensitivity of 71.1% and specificity of 69.2%. When the cut-off value for differentiating HCC from cirrhotic parenchyma was set at 0.95×10^{-3} mm^2/s, sensitivity and specificity were calculated as 62.2% and 80.4%, respectively.

Comparison with Child-Pugh Scores

A weak negative correlation was found between DWI-based ADC values and Child-Pugh scores (r=-0.396, p=0.008). No statistically significant correlation was found between ADC or FA values derived from DTI and Child-Pugh scores (p=0.695 and p=0.932, respectively).

Table 1. Clinical characteristics and laboratory data of the patients

Clinical factors and laboratory data	HCC group patients (n=62) (%)	Cirrhosis group patients (n=56) (%)
Sex		
Male	49 (79%)	37 (66.1%)
Female	13 (21%)	19 (33.9%)
Age (y, mean ± SD) (range)	65.1±8.2 (45-84)	58.7±11.2 (20-79)
Etiology		
HBV	37 (59.7%)	30 (53.6%)
HCV	3 (4.8%)	1 (1.8%)
Ethanol	8 (12.9%)	5 (8.9%)
HBV and ethanol	4 (6.5%)	2 (3.6%)
NASH	1 (1.6%)	1 (1.8%)
Cryptogenic or unknown etiology	8 (12.9%)	12 (21.4%)
Autoimmune hepatitis	1 (1.6%)	2 (3.6%)
Wilson disease	1 (1.8%)	
HBV-HDV coinfection	1 (1.8%)	
Primary biliary cirrhosis	1 (1.8%)	
Serum α-fetoprotein level (ng/mL) (mean ± SD)	1205.97±6117.35 (2-48000)	17.62±53.45 (1-350)
Cirrhosis	48 (77.4%)	56 (100%)
Child Pugh class		
A	31 (50%)	
B	20 (32%)	
C	9 (15%)	

HBV: Hepatitis B virus, HCC: Hepatocellular carcinoma, HCV: Hepatitis C virus, HDV: Hepatitis D virus, NASH: Non-alcoholic steatohepatitis, SD: Standard deviation, y: Years

Comparison Between Non-pathological Parenchyma and HCC

Patients with HCC had significantly lower ADC values and higher FA values compared to those with non-pathological parenchyma. Using a cut-off ADC value of 0.94×10^{-3} mm^2/s yielded a sensitivity of 33.9% (95% CI, 23.3-46.3) and specificity of 98.1% (95% CI, 89.9-99.7), with an area under the curve (AUC) of 0.656 (95% CI, 0.558-0.753). For FA, a threshold of 0.65 resulted in sensitivity and specificity of 38.7% (95% CI, 27.6-51.2) and 94.2% (95% CI, 81.8-97.0), respectively, with an AUC of 0.653 (95% CI, 0.554-0.751). In conventional DWI measurements, using a cut-off ADC value of 0.99×10^{-3} mm^2/s provided a sensitivity of 51.6% (95% CI, 39.4-63.6) and specificity of 69.2% (95% CI, 55.7-80.1), with an AUC of 0.688 (95% CI, 0.582–0.799). Group means are presented in Table 2 (Figure 2).

Comparison Between Cirrhotic Parenchyma and HCC

ADC values were significantly lower and FA values significantly higher in HCC lesions compared to cirrhotic parenchyma. Using a threshold of 1.07×10^{-3} mm^2/s for ADC, sensitivity and specificity were 56.5% (95% CI, 44.1-68.1) and 76.8% (95% CI, 64.2-85.9), respectively, with an AUC of 0.702 (95% CI, 0.603-0.794). For FA, a threshold of 0.43 yielded sensitivity and specificity of 62.9% (95% CI, 50.5-73.8) and 75.0% (95% CI, 62.3-84.5), respectively, with an AUC of 0.649 (95% CI, 0.542-0.745). In conventional DWI measurements, using a threshold of 0.95×10^{-3} mm^2/s provided a sensitivity of 62.2% (95% CI, 47.6-74.9) and specificity of 80.4% (95% CI, 68.2-88.7), with an AUC of 0.696 (95% CI, 0.579-0.803). No statistically significant difference was found in parenchymal DTI and FA measurements between HCC patients with or without underlying cirrhosis (p=0.832 and p=0.911, respectively) (Figure 3). Group means are presented in Table 3.

Comparison Between Cirrhotic and Non-pathological Liver Parenchyma

There was no statistically significant difference in DTI-ADC and FA values between cirrhotic and non-pathological liver parenchyma (p=0.469 and p=0.995, respectively).

Comparison Between HCC Lesion and Adjacent Non-tumoral Parenchyma

A paired sample t-test revealed significant differences between DTI-ADC and FA measurements obtained from HCC lesions and adjacent non-tumoral parenchyma in the same patients (p<0.009 and p=0.005, respectively). The corresponding mean values are summarized in Table 3.

DISCUSSION

In this preliminary study, ADC and FA values derived from DTI are presented in a relatively large cohort of patients with HCC. Our study was aimed to evaluate whether quantitative diffusion-based imaging parameters, particularly FA derived from DTI and ADC from conventional DWI, can reliably differentiate HCC from its surrounding parenchymal background. Rather than aiming to characterize the full radiologic spectrum of hepatic lesions, we focused on non-tumoral and cirrhotic liver tissue both clinically relevant comparators due to their established roles in the natural history and differential diagnosis of HCC. This design enabled us to investigate DTI's diagnostic performance within a well-defined and pathophysiologically coherent framework. Notably, unlike benign lesions, which are typically identified with high accuracy using conventional MRI protocols, cirrhotic liver parenchyma represents a diagnostically challenging substrate where subtle microstructural alterations may overlap with early tumorigenic changes. Therefore, establishing standardized DTI metrics in this context may serve as a crucial step toward integrating DTI into future multiparametric liver imaging strategies.

Table 2. Comparison of diffusion tensor imaging parameters between normal liver and HCC

	Non-pathological liver	HCC	p-value
ADC value (x 10^{-3} s/mm^2) (Mean ± SD)	1.14±0.13	1.04±0.22	<0.002
FA value (Mean ± SD)	0.40±0.07	0.46±0.14	0.004

ADC: Apparent diffusion coefficient, FA: Fractional anisotropy, HCC: Hepatocellular carcinoma, SD: Standard deviation

Table 3. Comparison of diffusion tensor imaging parameters between cirrhotic liver and HCC

	Cirrhotic liver	HCC	p-value
ADC value (x 10^{-3} s/mm^2) (Mean ± SD)	1.18±0.03	1.04±0.22	<0.001
FA value (Mean ± SD)	0.40±0.07	0.46±0.14	0.004

ADC: Apparent diffusion coefficient, FA: Fractional anisotropy, HCC: Hepatocellular carcinoma, SD: Standard deviation

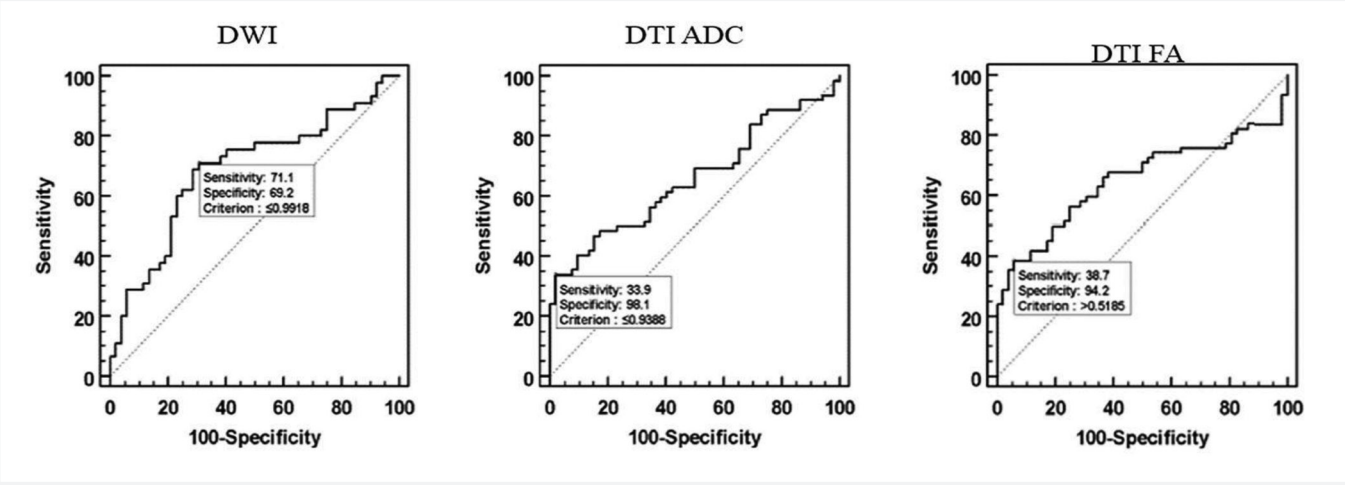

Figure 2. ROC curve on the group of patients with hepatocellular carcinoma and non-pathological liver parenchyma

DWI: Diffusion-weighted imaging, DTI: Diffusion tensor imaging, ADC: Apparent diffusion coefficient, FA: Fractional anisotropy

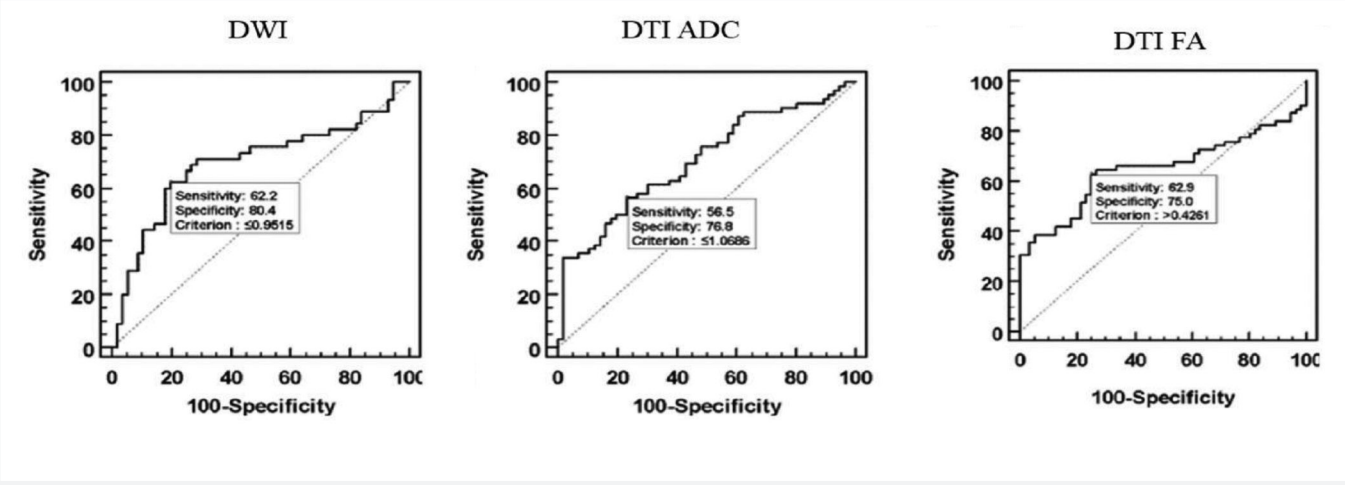

Figure 3. ROC curve on the group of patients with hepatocellular carcinoma and cirrhotic liver parenchyma.

DWI: Diffusion-weighted imaging, DTI: Diffusion tensor imaging, ADC: Apparent diffusion coefficient, FA: Fractional anisotropy

Although there are limited studies on the use of DTI in liver imaging, early findings suggest its potential utility[4-6,10-18]. Taouli et al.[6] reported that diffusion in non-pathological and cirrhotic liver parenchyma, as well as in focal hepatic lesions, was predominantly isotropic likely due to the liver's randomly organized microstructure, which contrasts with more structured organs like the brain or kidneys. In the same study, malignant lesions demonstrated lower ADC values than both benign lesions and liver parenchyma.

To date, only a limited number of studies have specifically investigated DTI findings in HCC[5,16-18]. Li et al.[5], using a 3T MRI system, focused on sequence optimization and the diffusion characteristics of HCC. Although our study was conducted at 1.5T, the observed diffusion patterns were largely comparable. While they recommended nine diffusion-encoding directions, we employed 20 to improve the accuracy and robustness of DTI[5].

Recent studies have further supported the clinical value of DTI in hepatic imaging, particularly for differentiating HCC from other hepatic lesions. In a study by Saleh et al.[16], FA and mean diffusivity (MD) were significantly lower in benign lesions compared to HCC, with FA values showing the highest diagnostic accuracy. Notably, FA >0.38 emerged as an independent predictor of HCC, outperforming both ADC and

MD in their regression model. These findings are in line with our observation that FA values in HCC are significantly elevated compared to non-malignant liver tissues, emphasizing the anisotropic nature of malignant lesions.

Mahmoud et al.[17] also demonstrated the diagnostic potential of liver DTI by comparing DTI-derived parameters with LI-RADS classification. They found a moderate positive correlation between FA and LI-RADS category, and a substantial negative correlation between DTI-ADC and LI-RADS, concluding that DTI-ADC and FA values perform better than conventional DWI-ADC in discriminating between benign and malignant lesions. This supports our findings, particularly in terms of the inverse relationship between FA and DTI-ADC values in malignant hepatic tissue.

Karim et al.[18] investigated the role of DTI in both lesion characterization and post-treatment response assessment. They reported that an FA cut-off value of >0.29 differentiated malignant from benign lesions with 95% sensitivity and 70% specificity.

In our study, which focused on distinguishing HCC from non-malignant parenchyma, we identified a higher optimal FA threshold of 0.43, yielding 62.9% sensitivity and 75% specificity. The lower sensitivity observed in our cohort may reflect the more subtle microstructural differences between malignant and cirrhotic tissues, as opposed to benign lesions, which are generally more isotropic. These variations highlight the importance of reference tissue selection and patient population characteristics in DTI analysis.

We found that the mean FA value in HCC (0.46±0.14) reflected moderate anisotropy, which was comparable to FA values in cirrhotic and non-pathological liver parenchyma (0.40±0.07). Although liver parenchyma is generally described as isotropic[6,7], the diffusion behavior of hepatic tumors remains controversial. Kinoshita et al.[19], in a study of malignant brain tumors, found a positive correlation between FA and both tumor cell density and Ki-67 index, suggesting that higher FA may reflect increased cellularity, although the biological basis for this relationship remains unclear.

Although our study demonstrated significantly higher FA values in HCC compared to non-pathological liver parenchyma, the relatively low sensitivity (38.7-62.9%) limits the stand-alone diagnostic utility of FA as a biomarker. This finding indicates that while elevated FA values can assist in suggesting malignancy, FA measurements alone may not reliably differentiate HCC in routine clinical practice. Therefore, FA should be interpreted alongside conventional MRI features and other quantitative diffusion parameters such as ADC. Future technical advances or multiparametric approaches may help overcome this limitation.

Study Limitations

This study has several limitations. First, its retrospective design may have introduced selection bias. Second, not all HCC and cirrhotic cases had histopathological confirmation; thus, the fibrosis stage in cirrhotic patients could not be evaluated. Third, ADC and FA measurements can vary depending on scanner hardware, observer expertise, and physiological motion. Previous reports have noted that cardiac motion can influence diffusion metrics, particularly in the left hepatic lobe, where systolic movement significantly elevates FA values[12]. To minimize motion artifacts, we focused our ROI placement on the posterior segment of the right lobe. While the majority of HCC lesions in our study were categorized as LI-RADS 5, a small number of LI-RADS 4 and indeterminate (LI-RADS 3) cases were also included. Although these cases were either histologically confirmed or supported by consensus diagnosis based on imaging features, their inclusion may introduce a degree of heterogeneity in diagnostic certainty, and should be considered when interpreting the results. Furthermore, the lack of significant difference in DTI measurements between cirrhotic and non-pathological parenchyma may reflect the heterogeneity of our cirrhosis group. Future studies should incorporate fibrosis grading and interobserver agreement analyses to better validate these findings.

CONCLUSION

In summary, this study demonstrated that DTI-derived parameters, particularly FA and ADC values, differ significantly between HCC lesions and non-lesional liver parenchyma. These findings suggest that DTI can provide additional microstructural information specific to HCC. However, the moderate sensitivity of FA measurements, and the absence of standardized acquisition protocols currently limit the clinical applicability of DTI as a stand-alone diagnostic tool. Rather than replacing conventional imaging criteria, DTI metrics should be considered complementary parameters that may enhance lesion characterization when used in conjunction with established MRI features. Future prospective studies involving larger, diverse patient populations and standardized imaging protocols are warranted to validate these preliminary findings and clarify the potential role of DTI in the non-invasive evaluation of HCC.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Trakya University Faculty of Medicine Scientific Research Ethics Committee (desicion no: 03/17, date: 03.02.2020).

Informed Consent: This is retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.K., Concept: C.Ö., D.K., N.T., Design: C.Ö., O.K., N.S., İ.K., Data Collection or Processing: C.Ö., B.S.S., N.S., İ.K., Analysis or Interpretation: O.K., N.S., Literature Search: C.Ö., B.S.S., D.K., O.K., İ.K., N.T., İ.K., N.T., Writing: C.Ö., B.S.S., D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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