RESEARCH ARTICLE

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# Diagnostic Value of Apparent Diffusion Coefficient in Differentiating Benign and Malignant Focal Liver Lesions

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## Abstract

**Objectives:** This study aims to evaluate the effectiveness of the apparent diffusion coefficient (ADC) in differentiating benign and malignant focal liver lesions (FLLs).

**Methods:** This study was conducted retrospectively on 87 patients who underwent liver magnetic resonance imaging (MRI). MRI of the patients was performed using a 1.5 Tesla Philips Intera MRI scanner. All ADC values of the lesions were measured using Radiant DICOM viewer software. The chi-square test, independent samples t-test, Mann-Whitney U test, and receiver operating characteristic analysis were used for statistical analysis.

**Results:** The patients included in the study were between 19 to 81 years of age, with a mean age of 52.6 (±14) years. While 51.7% (n=45) of the patients were female, 48.3% (n=42) were male. Benign lesions were detected in 54% (n=47) of the patients, while malignant lesions were found in 46% (n=40). The mean ADC values of malignant lesions were measured as $(0.95\pm0.37)\times10^{-3}$ mm²/s, and the mean ADC values of benign lesions were $(1.91\pm0.48)\times10^{-3}$ mm²/s, with a statistically significant difference between them ($p<0.001$). No statistically significant difference was found between the mean ADC values of hepatocellular carcinomas and metastases ($p=0.093$). The mean ADC value of focal nodular hyperplasias was calculated to be $(1.24\pm0.16)\times10^{-3}$ mm²/s, and the mean ADC value of hemangiomas was $(1.96\pm0.46)\times10^{-3}$ mm²/s, with a statistically significant difference between them ($p=0.012$). The optimal threshold value of ADC in distinguishing malignant lesions from benign ones was determined as $1.33\times10^{-3}$ mm²/s, with a sensitivity of 93% and a specificity of 90% (area under the curve=$0.959\pm0.019$, $p<0.001$).

**Conclusion:** ADC measurements, being an easily applicable and reproducible method, can effectively contribute to differentiating between benign and malignant liver lesions.

**Keywords:** Apparent diffusion coefficient, diffusion magnetic resonance imaging, focal liver lesion, magnetic resonance imaging

## Introduction

Focal liver lesions (FLLs) are defined as lesions with distinct borders in the liver parenchyma; which may be of benign or malignant origin. Benign lesions include hemangioma, adenoma, and focal nodular hyperplasia (FNH), while malignant lesions include hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and metastases.[1] Accurate differentiation of benign and malignant lesions is critical for early treatment planning and improving prognosis. In addition, accurate differentiation of lesions is important to prevent unnecessary invasive interventions in benign lesions.

Imaging methods play a crucial role in the diagnosis of FLLs. Ultrasonography, computed tomography, and magnetic resonance imaging (MRI) are commonly used methods for evaluating the morphological and functional characteristics of these lesions.[2] MRI particularly stands out in revealing different tissue characteristics with its soft tissue contrast and various sequences.[3,4] Furthermore, the ability to perform hepatobiliary phase studies with gadolinium contrast agents provides additional diagnostic superiority over MRI.[5] Among MRI sequences, diffusion-weighted imaging (DWI) has an important application in radiology, particularly in cancer patients.[6] Moreover, DWI enables the evaluation of diffuse liver diseases and the assessment of malignant tumors' response to treatment.[7]

Apparent diffusion coefficient (ADC) measurements obtained from DWI provide parametric data about lesions.[7] ADC is a parameter that evaluates tissue density and microstructure by measuring the Brownian

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motion of water molecules.[8] In DWI, ADC values can be quantitatively measured from tissues using at least two b-values.[9-11] ADC values are affected by factors such as cell density within tissue, intercellular space, necrosis areas, vascularity, and stromal structure.[3,5,8,12] Malignant lesions generally have denser cellular structures, limiting diffusion, which manifests as lower ADC values.[13-15] In contrast, benign lesions are associated with higher ADC values due to lower cell density and allowance for free movement of water molecules.[13-15] This difference suggests that ADC could be used as a biomarker in distinguishing benign from malignant lesions.

In the existing literature, the role of DWI and ADC values in characterizing normal tissues and various pathologies has been extensively studied.[16-19] Studies on the quantification of ADC values in FLLs have shown that this parameter can be used to differentiate between benign and malignant lesions.[6,13-15,20] However, some researchers have noted potential limitations regarding the diagnostic reliability of the method, reporting that overlap may be observed between ADC values of benign and malignant lesions.[14,21]

Despite advances in conventional MRI techniques, there remain significant diagnostic challenges in characterizing certain FLLs, particularly in cases where lesions demonstrate atypical enhancement patterns or in patients with chronic liver disease, where background parenchymal changes complicate interpretation. In these clinically ambiguous scenarios, ADC measurements can provide valuable additional information that may reduce the need for invasive diagnostic procedures such as biopsy. Furthermore, in patients with contraindications to contrast agents or in resource-limited settings where contrast-enhanced studies may not be readily available, ADC values could serve as an alternative diagnostic tool.

This study aims to investigate the diagnostic value of ADC in distinguishing between benign and malignant FLLs. In this context, the goal is to use ADC as a biomarker that can contribute to the clinical decision-making process.

## Methods

### Patient Selection

Patients included in our study were selected from those over 18 years of age who underwent dynamic liver MRI between March 2018 and March 2019. The inclusion criteria were determined as, complete dynamic liver MRI including DWI and ADC sequences, presence of FLL larger than 1 cm, and patient age above 18 years. Exclusion criteria were defined as: previous interventional procedures such as radiofrequency ablation of the liver lesion, history of local/systemic chemotherapy or radiotherapy treatment, and presence of artifacts in MRI that would limit evaluation. The FLLs initially planned to be included in the study were hemangioma, FNH, HCC, CCA, metastasis, and other rare liver lesions. Cysts were not included in the study as they are easily diagnosed. Pathology results were primarily considered in categorizing lesions into benign and malignant categories. Lesions without pathological diagnosis were categorized according to clinical and laboratory findings, as well as well-defined radiological imaging findings in the literature.[2,10] Consequently, using the inclusion and exclusion criteria, 87 patients were determined to be suitable for our study between the relevant dates. Patients' pathological diagnoses and demographic data were obtained from the hospital information management system.

### MRI and ADC Measurements of Patients

All cases included in the study underwent dynamic liver MRI using a 1.5 Tesla Philips Intera MRI scanner (Philips Healthcare, Best, the Netherlands). The MRI sequences in the imaging protocol were as follows: T1 weighted, in/out phase, T1 weighted (THRIVE), T2 weighted single-shot, Heavy T2 weighted single-shot, and DWI SSH EPI (Table 1). The b-values used in DWI examinations were b=0 s/mm$^2$, 200 s/mm$^2$, and 800 s/mm$^2$. The THRIVE sequence was performed before gadolinium chelate administration and at 30, 70, and 300 seconds after administration.

The liver MRI images of patients meeting the research criteria were comprehensively evaluated by a radiologist with 3 years of experience. Appropriate diagnoses were assigned to detected FLLs based on well-defined radiological imaging characteristics in the literature and pathology results. Subsequently, ADC values of FLLs were measured. ADC measurements were performed using Radiant DICOM (Digital Imaging and Communications in Medicine) viewer software (version 2020.2.3, 64-bit, Medixant, Poznań, Poland). Region of interest (ROIs) of 0.5 cm$^2$ were used for ADC measurements (Figures 1, 2). During measurements, possible areas of necrosis and hemorrhage within the lesions were identified using other sequences (e.g., T2-weighted) and excluded from the ROI. Additionally, care was taken to exclude vascular structures, normal liver parenchyma, and artifacts from the ROIs. Three separate ADC measurements were made for each lesion, and their average was recorded in the data collection form as the final ADC value of the lesion.

### Ethical Approval

Ethical approval for this retrospective study was obtained from the Non-interventional Research Ethics Committee of University of Health Sciences Türkiye (decision no: 18/319, date: 18.12.2018).

**Table 1. Sequences used in dynamic liver MRI**

| Sequences | Description of the sequence |
|---|---|
| T1w in/out phase | Axial plane images were obtained in-phase and out-of-phase using T1-weighted 2-dimensional gradient echo technique with breath-hold protocol. |
| T1w (THRIVE) | T1-weighted three-dimensional gradient echo sequence with fat suppression was obtained using volumetric interpolation technique with breath-hold protocol. |
| T2w single-shot | Axial plane T2-weighted single-shot turbo spin-echo images were obtained using half Fourier technique. |
| Heavy T2w single-shot | T2-weighted images were obtained in the axial plane using half Fourier technique with single-shot turbo spin-echo sequence. |
| DWI SSH EPI | Diffusion-weighted images were obtained under free breathing using echo-planar imaging technique and single-shot method with b-values of 0, 200, and 800 s/mm$^2$. |

w: Weighted, DWI: Diffusion-weighted imaging, SSH: Single-shot, EPI: Echo-planar imaging, THRIVE: T1 high-resolution isotropic volume examination, MRI: Magnetic resonance imaging

### Statistical Analysis

In the study, continuous variables such as age and ADC values were expressed as means and standard deviations. Categorical variables such as gender were expressed as numbers and percentages (%). The Kolmogorov-Smirnov test was used to evaluate whether continuous variables conformed to a normal distribution. The chi-square test was used to evaluate relationships between categorical variables. To test the difference in ADC values between malignant and benign lesions, an independent samples t-test was used for groups showing normal distribution, and Mann-Whitney U test was used for groups not showing normal distribution. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of ADC values in distinguishing between benign and malignant lesions. The area under the curve (AUC) was calculated using ROC analysis. A value of $p<0.05$ was accepted as the significance level in all statistical analyses. 95% confidence intervals (CI) were reported for estimated parameters. All analyses were performed using IBM Statistical Package for the Social Sciences 26 software (IBM Corporation, Armonk, NY, USA).

## Results

The ages of the 87 patients included in the study ranged from 19 to 81 years, with a mean age of 52.6 years (±14 years). 21.8% (n=19) of the patients were between 19 and 40 years, 47.2% (n=41) were between 41 and 60 years, and 31% (n=27) were between 61 and 81 years.

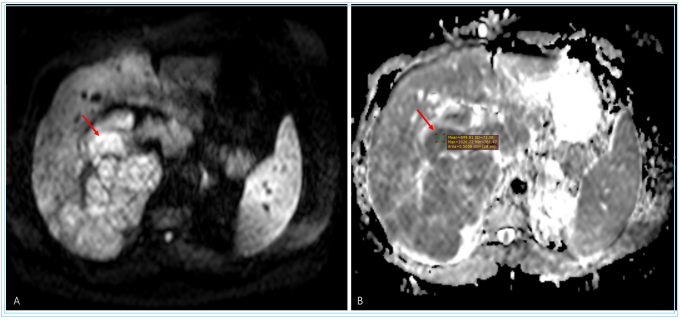

**Figure 1.** DWI (A) and ADC (B) images of a 46-year-old male patient with renal cell carcinoma metastasis in the liver. The lesion is localized in liver segment 7-8, appearing hyperintense on DWI and hypointense on ADC (arrow demonstrates an example ADC measurement)

*DWI: Diffusion-weighted image, ADC: Apparent diffusion coefficient*

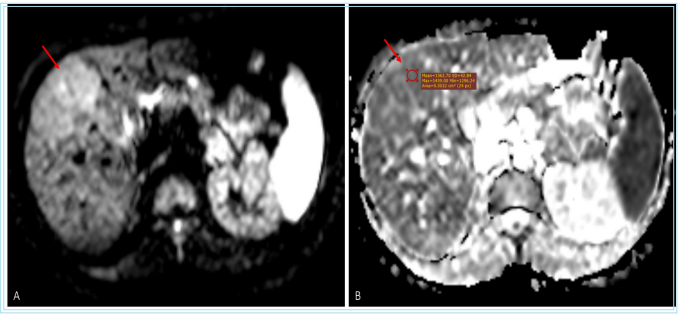

**Figure 2.** DWI (A) and ADC (B) images of a 19-year-old female patient with FNH in the liver. The lesion is localized in liver segment 8, appearing hyperintense on DWI and isointense on ADC (arrow demonstrates an example ADC measurement)

*DWI: Diffusion-weighted image, ADC: Apparent diffusion coefficient, FNH: Focal nodular hyperplasia*

When evaluated in terms of gender distribution, 51.7% (n=45) of the participants were female while 48.3% (n=42) were male (Table 2).

All malignant lesions (n=40) had a pathological diagnoses. Of these lesions, 82.5% (n=33) were metastases, 15% (n=6) were HCC, and 2.5% (n=1) was CCA. Among benign lesions (n=47), 6.4% (n=3) had a pathological diagnosis of FNH, while 93.6% (n=44) had a radiological diagnosis of hemangioma (Table 3).

The mean ADC value of all lesions in our study was measured as $(1.47\pm0.64)\times10^{-3}$ mm²/s. As a result of statistical analysis, the mean ADC value of malignant lesions was found to be $(0.95\pm0.37)\times10^{-3}$ mm²/s, which was significantly lower than the mean ADC value of benign lesions of $(1.91\pm0.48)\times10^{-3}$ mm²/s ($p<0.001$) (Table 4).

Accordingly, while the mean ADC value of 33 metastases was $(0.9\pm0.38)\times10^{-3}$ mm²/s, the mean ADC value of 6 HCCs was found to be $(1.18\pm0.21)\times10^{-3}$ mm²/s (Table 4). In the analysis performed with an

**Table 2. Demographic characteristics of patients**

| Demographic characteristics, n=87 | | n (%) |
|---|---|---|
| Age, (19-81 years)<br>Mean (±SD)=52.6 (±14) | 19-40 years | 19 (21.8) |
| | 41-60 years | 41 (47.2) |
| | 61-81 years | 27 (31) |
| Gender | Female | 45 (51.7) |
| | Male | 42 (48.3) |
| Total | | 87 (100) |

SD: Standart deviation

**Table 3. Distribution of focal liver lesions according to final diagnoses**

| | Lesion types | n (%) |
|---|---|---|
| Malign, n=40 | Metastasis* | 33 (82.5) |
| | HCC* | 6 (15) |
| | CCA* | 1 (2.5) |
| Benign, n=47 | Hemangioma** | 44 (93.6) |
| | FNH* | 3 (6.4) |
| Total | | 87 (100) |

*Diagnosis confirmed by pathological examination; **Diagnosis based on radiological imaging.
HCC: Hepatocellular carcinoma, CCA: Cholangiocellular carcinoma, FNH: Focal nodular hyperplasia

**Table 4. Comparison of ADC values between benign and malignant lesions and their subtypes**

| | n (%) | ADC value, ($\times10^{-3}$ mm²/s) | p |
|---|---|---|---|
| | | Mean (±SD) | |
| Benign | 47 (54) | 1.91 (±0.48) | **<0.001** |
| Malign | 40 (46) | 0.95 (±0.37) | |
| Metastasis | 33 (82.5) | 0.9 (±0.38) | 0.093* |
| HCC | 6 (15) | 1.18 (±0.21) | |
| Hemangioma<br>FNH | 44 (93.6)<br>3 (6.4) | 1.96 (±0.46)<br>1.24 (±0.16) | **0.012**** |
| Total | 87 (100) | 1.47 (±0.64) | |

*Independent samples t-test; **Mann-Whitney U test.
ADC: Apparent diffusion coefficient, HCC: Hepatocellular carcinoma, FNH: Focal nodular hyperplasia, SD: Standard deviation

independent samples t-test, no statistically significant difference was found between the ADC values of HCC and metastases (p=0.093). Due to the insufficient number of CCA (n=1, 2.5%), it was not included in the statistical comparison analyses. Among benign lesions, the mean ADC value of 44 hemangiomas was calculated as (1.96±0.46)×10$^{-3}$ mm$^2$/s, which was higher than the mean ADC value of 3 FNHs, which was (1.24±0.16)×10$^{-3}$ mm$^2$/s (Table 4). This difference was found to be statistically significant (p=0.012).

An ROC analysis was performed to evaluate the diagnostic performance of ADC values in distinguishing malignant from benign lesions (Figure 3). The optimal threshold value of ADC in distinguishing malignant lesions from benign ones was determined as 1.33×10$^{-3}$ mm$^2$/s, and at this value, the sensitivity of the test was 93% and the specificity was 90%. The 95% CI of the obtained results ranges from 0.922 to 0.996. As a result of the analysis, the AUC was calculated as 0.959±0.019, and this value was found to be statistically significant (p<0.001).

## Discussion

MRI is frequently used in clinical practice for detecting FLLs and shows a high success rate in diagnosis. However, MRI can sometimes be challenging in distinguishing between malignant and benign lesions. Our study demonstrates that ADC measurements can differentiate between malignant and benign FLLs and contribute to diagnosis. The most important results of our study are as follows. First, in our study, the mean ADC value of malignant lesions was found to be significantly lower than benign lesions. Second, using a threshold value of 1.33×10$^{-3}$ mm$^2$/s resulted in high sensitivity and specificity values for distinguishing malignant lesions from benign ones. There is no significant difference between the mean ADC values of malignant lesion subtypes (metastasis and HCC). Among benign lesions, the mean ADC value of FNH is significantly lower than that of hemangiomas.

In our study, the mean ADC value of malignant lesions was found to be (0.95±0.37)×10$^{-3}$ mm$^2$/s. This value is consistent with similar studies in the literature. Surov et al.[3] found the mean ADC values of malignant lesions to be (0.93±0.30)×10$^{-3}$ mm$^2$/s, Battal et al.[22] (0.86±0.13)×10$^{-3}$ mm$^2$/s, Demir et al.[23] (0.86±0.11)×10$^{-3}$ mm$^2$/s, and Kim et al.[24] (1.01±0.38)×10$^{-3}$ mm$^2$/s.

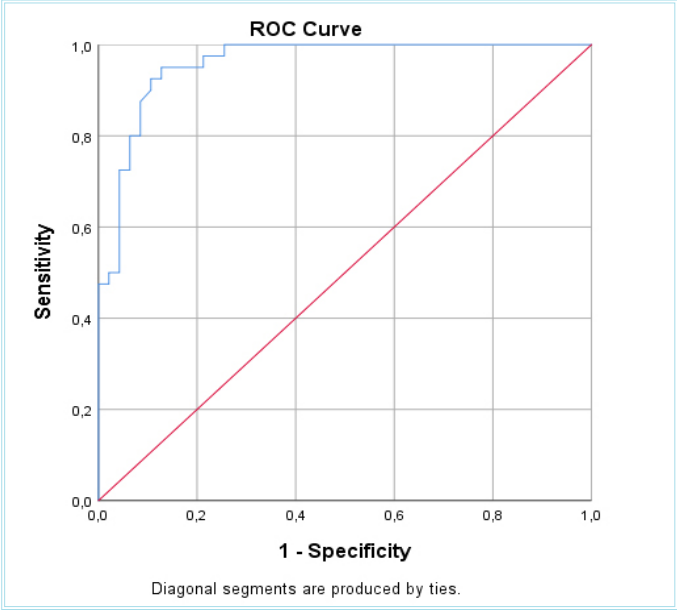


**Figure 3.** ROC analysis performed to evaluate the diagnostic ability of ADC values to distinguish malignant lesions from benign lesions

*ROC: Receiver operating characteristic, ADC: Apparent diffusion coefficient*

In our study, while the mean ADC value of metastases among malignant lesions was (0.9±0.38)×10$^{-3}$ mm$^2$/s, the mean ADC value of HCCs was found to be (1.18±0.21)×10$^{-3}$ mm$^2$/s, and no statistically significant difference was found between these values (p=0.093). Different results regarding ADC values of malignant lesions have been reported in comparative studies in the literature. Taouli et al.[10] reported ADC values as (0.94±0.6)×10$^{-3}$ mm$^2$/s in metastases and (1.33±0.13)×10$^{-3}$ mm$^2$/s in HCCs. In the study by Kim et al.,[24] ADC values were found to be (1.06±0.5)×10$^{-3}$ mm$^2$/s in metastases and (0.97±0.31)×10$^{-3}$ mm$^2$/s in HCCs. Similar to our study, the difference between mean ADC values of metastases and HCCs was not found to be statistically significant in the studies by Bruegel et al.,[7] Kim et al.,[24] Namimoto et al.,[25] and Kilickesmez et al.[26]

In our study, the mean ADC value of benign lesions was found to be (1.91±0.48)×10$^{-3}$ mm$^2$/s, which was consistent with the value reported by Battal et al.[22] (1.94±0.61)×10$^{-3}$ mm$^2$/s. Additionally, Kim et al.[24] reported mean ADC values of benign lesions as (2.49±1.39)×10$^{-3}$ mm$^2$/s, and Jahic et al.[6] as 1.88 (1.326 to 2.48)×10$^{-3}$ mm$^2$/s.

In our study, the mean ADC value of FNHs was found to be (1.24±0.16)×10$^{-3}$ mm$^2$/s, which was statistically significantly lower than the mean ADC value of hemangiomas (1.96±0.46)×10$^{-3}$ mm$^2$/s (p=0.012). ADC measurements were found to show excellent diagnostic performance in FNH-hemangioma differentiation. In previous studies, Cieszanowski et al.,[27] reported ADC values of hemangiomas as 1.55 (1.46-1.64)×10$^{-3}$ mm$^2$/s, Taouli et al.,[10] as (2.95±0.67)×10$^{-3}$ mm$^2$/s, and Gourtsoyianni et al.,[28] as 1.90 (1.56-2.24)×10$^{-3}$ mm$^2$/s. In our study, the mean ADC value of hemangiomas falls between these values. In previous studies, Cieszanowski et al.[27] reported the mean ADC value of FNHs as 1.18 (0.99-1.36)×10$^{-3}$ mm$^2$/s, Bruegel et al.[7] as (1.40±0.15)×10$^{-3}$ mm$^2$/s, and Parikh et al.[29] as (1.49±0.49)×10$^{-3}$ mm$^2$/s. In our study, the mean ADC value of FNHs falls between these reported values. Although FNHs are benign lesions, they can restrict diffusion due to their hypercellular internal structure, which emerges as one of the most important situations causing confusion in diagnosis.

In our study, the mean ADC values of malignant lesions were found to be significantly lower compared to benign lesions (p<0.001). In other studies in the literature, ADC values of malignant lesions are also significantly lower than those of benign lesions.[10,22,24,29]

In our ROC analysis, the optimal threshold value of ADC in distinguishing malignant lesions from benign ones was determined as 1.33×10$^{-3}$ mm$^2$/s, with a sensitivity of 93% and a specificity, of 90% at this point. In the study by Battal et al.,[22] the threshold ADC value was found to be 1.21×10$^{-3}$ mm$^2$/s, indicating that malignant lesions could be distinguished from benign ones with 100% sensitivity and 89.3% specificity at this value. In Parikh et al.'s[29] study, the threshold value was determined as 1.6×10$^{-3}$ mm$^2$/s, stating that malignant lesions could be distinguished from benign ones with 74.2% sensitivity and 77.3% specificity. Possible reasons for reporting different threshold values in benign-malignant lesion differentiation in similar studies in the literature include imaging device, used sequence parameters, number of b-values taken, maximum b-factor, patient population, lesion sizes, and differences between observers.[30]

DWI has a wide range of clinical applications. It is not only a highly useful imaging method in detecting liver lesions, but also particularly stands out in detecting and monitoring ischemic stroke.[31,32] Besides these, it is used in the diagnosis of many malignancies such as brain tumors.[33] prostate cancer detection,[34] and rectal cancer detection.[35] In addition to tumor detection, DWI can also be used in tumor characterization and evaluation of treatment response.[9,36] Furthermore, DWI is a highly useful imaging method in distinguishing non-malignant lesions such as abscesses from cystic/necrotic tumors.[36]

Despite DWI's potential in tumor detection and characterization, there are various obstacles to its widespread use. These obstacles include a lack of standardization in imaging protocols, such as the b-values used, and difficulties in evaluating tumor heterogeneity.[9] Additionally, differences between evaluators can be considered another obstacle.[9] To overcome these limitations, integration of ADC measurements into routine clinical practice should be strongly encouraged, supported by clearly defined threshold values. Based on our findings, we recommend using the threshold value of $1.33\times10^{-3}$ $mm^2/s$ as a complementary diagnostic tool, especially when conventional imaging findings are ambiguous. However, ADC values must always be interpreted alongside other imaging findings and clinical context due to possible overlaps between pathologies such as FNH and HCC. Most importantly, the establishment of standardized acquisition protocols with consistent b-values across different MRI systems and institutions is crucial. Such standardization would significantly enhance reproducibility, facilitate reliable comparisons of ADC measurements between centers, and ultimately improve the diagnostic accuracy and clinical utility of this non-invasive biomarker for the characterization of FLLs. Increasing awareness and training among radiologists regarding ADC interpretation can further support effective implementation in daily practice.

### Study Limitations

Our study has several limitations. The first limitation is the inability to evaluate lesions with low incidence, such as lymphoma, adenoma, and abscess, in our study. Second on the list is the inability to obtain pathological diagnoses of hemangiomas among benign lesions. However, the well-defined radiological findings of hemangiomas reduce the need for histopathological verification in diagnosing these lesions. Third, the exclusion of lesions smaller than 1 cm is another limitation of our study. This exclusion criterion prevents the evaluation of ADC's diagnostic potential in early-stage lesions, which is particularly important for timely detection of malignancies. Future studies should aim to include smaller lesions to assess the reliability and diagnostic accuracy of ADC measurements in these cases, while addressing technical challenges such as partial volume effects and motion artifacts that may affect the accuracy of such measurements. Additionally, the relatively small sample size of our study, particularly within specific subgroups of lesions, is an important limitation that may affect the generalizability of our findings. The presence of only one case of CCA necessitated its exclusion from statistical comparisons. Future studies should aim to include representation of different histopathological subtypes, particularly rare lesions like CCA, to enable more comprehensive statistical analyses, and potentially improve the diagnostic utility of ADC values across a wider spectrum of FLLs. Our results should be validated in larger, multi-center studies before being widely applied in clinical practice. Studies with larger sample sizes are needed to validate the results and establish more definitive diagnostic thresholds.

## Conclusion

In conclusion, it has been determined that ADC, which is an easily applicable and reproducible method, can effectively assist distinguishing between benign and malignant focal lesions detected in the liver.

### Ethics

**Ethics Committee Approval:** Ethical approval for this retrospective study was obtained from the Non-interventional Research Ethics Committee of University of Health Sciences Türkiye (decision no: 18/319, date: 18.12.2018).

**Informed Consent:** Because this was a retrospective study, informed consent was not required by the ethics committee.

### Footnotes

### Authorship Contributions

Concept: E.A., Design: E.A., Data Collection or Processing: E.A., Analysis or Interpretation: E.A., Literature Search: E.A., M.K., K.N.A., Writing: E.A., M.K., K.N.A.

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

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