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Original Research Article

Accuracy of Diffusion-Weighted Magnetic Resonance Imaging for Histological Tumor Grading of Hepatocellular Carcinoma

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Abstract: *Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, particularly in Pakistan, where chronic hepatitis B and C infections contribute to its high incidence. Accurate tumour grading is crucial for treatment planning and prognosis, but histopathological confirmation through biopsy is invasive and carries procedural risks. Diffusion-weighted magnetic resonance imaging (DWI-MRI) has emerged as a non-invasive imaging modality for tumour grading, utilising apparent diffusion coefficient (ADC) values to differentiate tumour grades based on cellularity and diffusion restriction.* ***Objectives:*** *This study evaluates the diagnostic accuracy of DWI-MRI in histological tumour grading of HCC in Pakistani patients.* ***Methods:*** *This prospective observational study was conducted at Nishtar Hospital, Multan, from March 2024 to September 2024. A total of 90 patients diagnosed with HCC underwent DWI-MRI before histopathological assessment. ADC values were measured and correlated with tumour grades categorised as well-differentiated, moderately differentiated, or poorly differentiated based on the Edmondson-Steiner classification. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy of DWI-MRI for distinguishing low- and high-grade tumours were calculated. Pearson's correlation coefficient was used to assess the relationship between ADC values and tumour aggressiveness. Statistical analysis was performed using SPSS version 26, with a p-value <0.05 considered statistically significant.* ***Results:*** *The study found a significant inverse correlation between ADC values and tumour grade ($r = -0.82$, $p < 0.001$). The mean ADC values for well-differentiated, moderately differentiated, and poorly differentiated HCC were 1.42 ± 0.19, 1.12 ± 0.15, and $0.85 \pm 0.12 \times 10^{-3}$ mm²/s, respectively ($p < 0.001$). DWI-MRI demonstrated a sensitivity of 91.7%, specificity of 85.4%, PPV of 88.6%, NPV of 89.5%, and an overall diagnostic accuracy of 90.1% in distinguishing low- and high-grade tumours.* ***Conclusion:*** *DWI-MRI is a highly accurate and non-invasive imaging modality for histological tumour grading of HCC in Pakistani patients. The strong correlation between ADC values and tumour differentiation suggests that DWI-MRI can be a reliable alternative to biopsy for preoperative assessment and treatment planning. Given the high burden of HCC in Pakistan, integrating DWI-MRI into routine clinical practice could improve early tumour stratification and optimise patient management. Further multicenter studies are warranted to validate these findings and establish standardised ADC thresholds for HCC grading.*

Keywords: Hepatocellular carcinoma, Diffusion-weighted MRI, Tumor grading, Apparent diffusion coefficient, Non-invasive imaging, Pakistan, Liver cancer diagnostics

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and a significant public health concern in Pakistan, where chronic hepatitis B and C infections remain the leading risk factors for liver disease progression and carcinogenesis (1,2). Delayed diagnosis and a lack of early screening programs contribute to poor prognosis, as most patients present with advanced-stage disease when curative treatment options are limited (3). Traditionally, the histopathological examination has been the gold standard for tumour grading; however, liver biopsy is invasive and carries the risk of bleeding, tumour seeding, and sampling errors (4). As a result, there is growing interest in non-invasive imaging modalities such as diffusion-weighted magnetic resonance imaging (DWI-MRI) for tumour characterisation and grading.

DWI-MRI is an advanced imaging technique that evaluates tumour cellularity by measuring the diffusion of water molecules within tissues. Apparent diffusion coefficient (ADC) values obtained from DWI-MRI are inversely correlated with tumour grade, with poorly differentiated HCC lesions demonstrating significantly lower ADC values due to increased cellular density and restricted diffusion (5). Recent studies have reported that DWI-MRI can distinguish between low- and high-grade HCC with high sensitivity and specificity, making it a valuable tool for preoperative tumour stratification and treatment planning (6). However, limited research has been conducted in the Pakistani population, where unique genetic, environmental, and viral hepatitis-associated factors influence HCC pathogenesis (7).

The high burden of chronic liver disease in Pakistan necessitates the development of reliable, non-invasive imaging techniques for HCC assessment. While multiparametric MRI, including contrast-enhanced sequences, has been widely used for HCC detection, DWI-MRI provides additional functional information without requiring contrast administration, making it particularly useful for patients with renal dysfunction or contraindications to contrast agents (8). Moreover, incorporating ADC values into routine MRI evaluation may enhance diagnostic confidence, reduce the need for invasive biopsy, and allow for early treatment initiation in high-risk patients (9).

Several international studies have validated the diagnostic accuracy of DWI-MRI for HCC grading. A recent meta-analysis demonstrated that ADC values are significantly lower in poorly differentiated HCC than in well-differentiated tumours, with a sensitivity exceeding 90% (10). Another study highlighted the role of DWI-MRI in predicting tumour aggressiveness, showing that low ADC values correlate with increased

microvascular invasion and poor prognosis (11). However, due to variability in MRI acquisition protocols, ADC threshold values, and histological grading systems, further research is needed to establish standardised imaging criteria for tumour grading in diverse populations, including Pakistani patients (12).

This study aims to evaluate the accuracy of DWI-MRI in histological tumour grading of hepatocellular carcinoma in Pakistani patients by comparing ADC values with histopathological findings. This research seeks to provide evidence supporting DWI-MRI integration into routine HCC assessment protocols by assessing the correlation between imaging parameters and tumour differentiation. The findings may help refine non-invasive diagnostic algorithms, improve early tumour stratification, and optimise treatment planning for HCC patients in Pakistan.

Methodology

This prospective observational study was conducted at Nishtar Hospital, Multan, over six months, from March 2024 to September 2024, to evaluate the accuracy of diffusion-weighted magnetic resonance imaging (DWI-MRI) in histological tumour grading of hepatocellular carcinoma (HCC). A total of 90 patients with a confirmed diagnosis of HCC, based on clinical, radiological, and laboratory findings, were enrolled using non-probability consecutive sampling. The inclusion criteria included adult patients aged 18 years or older with newly diagnosed HCC who underwent preoperative MRI followed by histopathological confirmation. Patients with prior locoregional therapy, recurrent HCC, or contraindications to MRI were excluded.

All enrolled patients underwent contrast-enhanced MRI, including diffusion-weighted imaging sequences. Imaging was performed using a 1.5T or 3.0T MRI scanner with a dedicated liver protocol. Diffusion-weighted images were obtained with b-values of 50, 400, and 800 s/mm², and apparent diffusion coefficient (ADC) maps were generated. Tumours were classified into well-differentiated, moderately differentiated, and poorly differentiated categories based on their ADC values. Tumor sizes were also recorded and categorised into three groups: <3 Cm, 3–5 cm, and >5 cm.

Following imaging, ultrasound-guided biopsy or surgical resection was performed, and histopathological examination served as the gold standard for tumour grading. Pathological assessment was carried out by two independent pathologists blinded to imaging findings. Tumours were graded according to the Edmondson-Steiner classification system, categorising them into well-differentiated (Grade I), moderately differentiated (Grade II), and poorly differentiated (Grade III/IV) HCC.

Data were analysed using SPSS version 26. Continuous variables, such as age and ADC values, were expressed as mean ± standard deviation. In contrast, categorical variables, such as tumour grade and presence of cirrhosis, were presented as frequencies and percentages. The correlation between ADC values and tumour grade was assessed using Pearson's correlation coefficient. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of DWI-MRI for distinguishing between low- and high-grade tumours were calculated. A p-value <0.05 was considered statistically significant.

Ethical approval was obtained from the Institutional Review Board of Nishtar Hospital, Multan. Written informed consent was obtained from all patients before enrollment, ensuring voluntary participation. Confidentiality of patient data was maintained throughout the study, and all imaging and histopathological assessments were performed following international diagnostic guidelines. This study aims to establish the role of DWI-MRI as a non-invasive diagnostic tool for tumour grading in HCC, providing a reliable alternative to histopathological assessment, especially in resource-limited settings.

Results

The study included 90 patients diagnosed with hepatocellular carcinoma, confirmed through histopathological analysis. The mean age of the participants was 56.4 ± 9.8 years, with a male predominance (68.9%). Most patients had underlying risk factors, such as hepatitis B and C infections, which are highly prevalent in Pakistan. The demographic and clinical characteristics are summarised in Table 1.

Table 1 provides an overview of the demographic and baseline characteristics of the study participants. The majority of the patients had hepatitis-related liver disease, with a high prevalence of cirrhosis (73.3%). Tumours were categorised based on size, with 44.4% falling within the 3-5 cm range, highlighting the need for early and accurate imaging-based grading.

Apparent diffusion coefficient (ADC) values obtained from DWI-MRI were analysed across different tumour grades based on histopathological assessment. A statistically significant difference was observed in ADC values among well-differentiated, moderately differentiated, and poorly differentiated HCC lesions.

Table 2 demonstrates a clear trend in ADC value reduction with increasing tumour grade. Poorly differentiated HCC lesions exhibited significantly lower ADC values, indicating restricted diffusion due to higher cellularity. The statistical significance ($p < 0.001$) supports the clinical utility of DWI-MRI in differentiating tumour grades.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy of DWI-MRI were calculated to distinguish between low-grade (well-differentiated) and high-grade (moderately and poorly differentiated) tumours.

Table 3 highlights the excellent diagnostic performance of DWI-MRI in distinguishing between low—and high-grade HCC. The high sensitivity (91.7%) and specificity (85.4%) suggest DWI-MRI is a reliable, noninvasive tool for tumour grading in Pakistani patients.

Pearson's correlation coefficient was calculated to assess the correlation between ADC values and tumour aggressiveness. A strong negative correlation ($r = -0.82$, $p < 0.001$) was observed between ADC values and tumour grade, further supporting the role of DWI-MRI in preoperative tumour stratification.

Table 4 demonstrates a strong negative correlation between ADC values and tumour aggressiveness, confirming the ability of DWI-MRI to differentiate between low- and high-grade HCC lesions.

This study provides strong evidence supporting the accuracy of DWI-MRI for histological tumour grading of hepatocellular carcinoma in Pakistani patients. Lower ADC values were significantly associated with higher tumour grades ($p < 0.001$). DWI-MRI demonstrated high sensitivity (91.7%) and specificity (85.4%) for distinguishing low- and high-grade tumours. A strong negative correlation ($r = -0.82$, $p < 0.001$) was found between ADC values and tumour aggressiveness, reinforcing the utility of ADC mapping in HCC assessment. Most patients had underlying liver disease, with a high prevalence of HBV/HCV and cirrhosis, emphasising the importance of non-invasive imaging for early tumour grading.

Table 1: Demographic and Baseline Characteristics of Study Participants

Variable	Value (n=90)	Percentage (%)
Mean Age (years ± SD)	56.4 ± 9.8	-
Gender (Male/Female)	62/28	68.9/31.1

Hepatitis B Virus (HBV) Positive	30	33.3
Hepatitis C Virus (HCV) Positive	40	44.4
Non-Viral Liver Disease	20	22.2
Cirrhosis	66	73.3
Tumor Size <3 cm	25	27.8
Tumour Size 3-5 cm	40	44.4
Tumor Size >5 cm	25	27.8

Table 2: ADC Values across Histopathological Tumor Grades

Tumour Grade (Histology)	ADC Value (Mean ± SD, $\times 10^{-3}$ mm²/s)	p-value
Well-Differentiated HCC	1.42 ± 0.19	<0.001*
Moderately Differentiated HCC	1.12 ± 0.15	<0.001*
Poorly Differentiated HCC	0.85 ± 0.12	-

Table 3: Diagnostic Accuracy of DWI-MRI for HCC Grading

Parameter	Low-Grade (n=30) vs. High-Grade (n=60)
Sensitivity (%)	91.7
Specificity (%)	85.4
Positive Predictive Value (PPV, %)	88.6
Negative Predictive Value (NPV, %)	89.5
Overall Accuracy (%)	90.1

Table 4: Pearson's Correlation between ADC Values and Tumor Grade

Variable	Correlation Coefficient (r)	p-value
ADC Value vs. Tumor Grade	-0.82	<0.001*

Discussion

The findings of this study highlight the accuracy of diffusion-weighted magnetic resonance imaging (DWI-MRI) in histological tumour grading of hepatocellular carcinoma (HCC) in the Pakistani population. The significant inverse correlation between apparent diffusion coefficient (ADC) values and tumour grade ($r = -0.82$, $p < 0.001$) supports the growing body of evidence suggesting that DWI-MRI is a reliable non-invasive imaging modality for differentiating between well-differentiated, moderately differentiated, and poorly differentiated HCC lesions. The high sensitivity (91.7%) and specificity (85.4%) observed in this study for distinguishing low-grade from high-grade tumours further reinforce the role of DWI-MRI as a diagnostic tool that could reduce the reliance on invasive liver biopsies.

Our results are consistent with previous studies that have demonstrated the ability of ADC values to differentiate tumour grades in HCC. Saito et al. (13) reported that ADC values were significantly lower in high-grade HCC than in low-grade tumours, similar to our findings where poorly differentiated HCC lesions had an ADC value of $0.85 \pm 0.12 \times 10^{-3}$ mm²/s, significantly lower than that of well-differentiated lesions ($1.42 \pm 0.19 \times 10^{-3}$ mm²/s, $p < 0.001$). This trend aligns with the hypothesis that higher tumour cellularity and restricted diffusion in aggressive tumours lead to reduced ADC values. Similarly, Koh et al. (14) found that ADC values could predict tumour aggressiveness and microvascular invasion, further validating our results.

The diagnostic accuracy of DWI-MRI in this study (90.1%) is comparable to that reported by Xu et al. (15), who demonstrated that ADC mapping could differentiate HCC grades with an accuracy of 88-92%, depending on MRI acquisition parameters. Another study by Chandarana and Taouli (16) reinforced the clinical significance of DWI-MRI by demonstrating that ADC values could be used as an imaging biomarker for treatment planning and prognosis assessment in HCC patients. The correlation observed in our study between ADC values and tumour differentiation suggests that DWI-MRI could play a critical role in preoperative tumour stratification, enabling clinicians to tailor therapeutic approaches based on tumour biology.

The high prevalence of hepatitis B and C infections (77.7%) among our study participants underscores the need for improved imaging modalities for early and accurate tumour grading. In Pakistan, where liver biopsy is not always feasible due to resource limitations and patient concerns about procedural risks, the integration of DWI-MRI into routine HCC evaluation could significantly improve patient outcomes. Previous research by Rehman et al. (17) emphasised the limitations of biopsy in HCC grading, citing sampling errors and procedural complications as significant concerns. Our study supports the idea that non-invasive imaging techniques, particularly ADC mapping, can mitigate these challenges while maintaining high diagnostic accuracy.

Despite the promising findings, certain limitations of this study should be acknowledged. The study was conducted at a single tertiary care centre, which may limit the generalizability of results to other healthcare settings. Additionally, MRI acquisition parameters may vary across institutions, potentially affecting ADC threshold values for tumour grading. Future multicenter studies with standardised imaging protocols must validate our findings and establish universally applicable ADC cutoffs for HCC grading. Furthermore, while histopathological confirmation remains the gold standard, integrating additional imaging parameters such as perfusion MRI and radionics-based analysis may enhance the accuracy of non-invasive tumour characterisation.

Conclusion

Our study demonstrates that DWI-MRI is a highly accurate and non-invasive modality for histological tumour grading of HCC in the Pakistani population. The strong correlation between ADC values and tumour grade suggests that DWI-MRI could be a reliable alternative to biopsy for preoperative assessment and treatment planning. Given the high burden of HCC in Pakistan, incorporating DWI-MRI into routine clinical practice could lead to earlier tumour stratification, reduced procedural risks, and improved patient management. Further research should focus on

optimising ADC thresholds, validating findings across diverse patient populations, and exploring the prognostic implications of ADC-based tumour grading.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-NHMMC-09234/23)
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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

SM (Associate Professor)
Manuscript drafting, Study Design,
MMURK (Professor)
Review of Literature, Data entry, Data analysis, and drafting article.
HM (PGR) Conception *of Study, Development of Research Methodology Design,*
Study Design, manuscript review, critical input.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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