ROLE OF MEAN APPARENT DIFFUSION COEFFICIENT (ADC) VALUE IN DIFFERENTIATION OF HIGH- AND LOW-GRADE GLIOMAS ON CONTRAST-ENHANCED MRI

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ABSTRACT

Objectives: The purpose of our study was to determine the role of mean apparent diffusion coefficient (ADC) values in differentiating low-grade from high-grade gliomas, keeping conventional MRI sequences as a gold standard

Material & Methods: This study was done in Lady Reading Hospital from September 2022 to December 2023. The prospective cross-sectional descriptive study included patients from the Out-Patient Department and Neurosurgery wards. Patients underwent MRI on a 1.5 Tesla machine, acquiring T2WI, T1WI, FLAIR, DWI, and gadolinium-enhanced T1WI sequences. PACS software identified areas with restricted diffusion and low ADC values. ROI measurements were made to determine ADC values. Image artifacts and contrast enhancement patterns were noted. Data on patient demographics, lesion location, MRI features, and ADC values were analyzed with SPSS-23.

Results: A total of 104 patients were included, with ages ranging from 3–87 years (Mean 41 years, ± 19.5), with 62 having low-grade gliomas and 42 high-grade gliomas. The mean ADC values were 1334.37 ± 300.85 mm2/s for low-grade and 842.88 ± 232.013 mm2/s for high-grade gliomas. The sensitivity and specificity of low ADC for high-grade glioma are 83.33 % and 77.42%, respectively. The optimal ADC cut of 1086.58 mm2/s significantly correlated with glioma grading ($p < 0.001$). Multiple linear regression revealed a significant relationship ($p < 0.001$) between mean ADC and tumor enhancement. Notable associations between ADC cut-off and enhancement were identified ($p = 0.001$).

Conclusion: The ADC values serve as a non-invasive and reliable radiological marker in distinguishing low-grade and high-grade gliomas. They improve the diagnostic accuracy of conventional MRI and aid in preoperative decision-making, reducing the need for invasive tissue biopsy.

Keywords: ADC, gliomas, MRI, peritumoral edema, tumor enhancement.

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INTRODUCTION

Gliomas constitute 26% of all primary brain tumors and 81% of malignant central nervous system tumors. [1] The World Health Organization (WHO) tumor classification categorizes gliomas into four grades, where grades I–II are low-grade gliomas (LGGs) with better prognosis and longer life expectancy. Whereas grades III–IV are highly aggressive and thus categorized as high-grade glioma (HGGs), they have a poor prognosis despite therapeutic procedures. [2] The standard treatment for gliomas is surgical removal.

Postoperatively, LGGs are only followed and observed closely, while HGG requires adjuvant therapy with radiation and chemotherapy to prevent recurrence. [3] Complete resections of HGG are critical due to their high malignant potential, and thus, assessment of tumor grade and infiltration into surrounding tissue preoperatively is of utmost significance for intraoperative decision-making. [4] Histopathological grading has its major limitation of being an invasive procedure.

It is also prone to sampling error as it proliferates by infiltration, and thus, the region of highest malignancy and the most vascular part of the tumor may lie with-

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in the peri-tumoral or peri-enhancing. [5] These limitations raise the need for further research into refining noninvasive methods for accurate preoperative assessment of gliomas. The WHO Classification of Tumors of the Central Nervous System Fifth Edition (WHO CNS5) encourages the use of molecular characteristics for the diagnosis and grading of gliomas. [6]

Conventionally done contrast-enhanced MRI is the gold standard among non-invasive techniques for glioma grading. [7] Avid contrast enhancement, peritumoral edema, mass effect, heterogeneous signal, central necrosis, and hemorrhage within the tumor are characteristics of HGGs. Low-grade gliomas appear as a relatively homogeneous mass with well-defined margins, minimal or no vasogenic edema, and little or no contrast enhancement. [8] With technological development, newer MRI techniques like diffusion-weighted imaging (DWI) have been used to grade gliomas. DWI gives information about tumor cellularity, which in turn predicts the tumor grade. [9]

Additionally, the apparent diffusion coefficient (ADC) value of a tumor provides more accurate information compared to conventional MRI, correlating well with the histopathological grade. The ADC sequence utilizes the diffusion of water molecules within tissue. [10] Due to heterogeneous micro-architecture, diseased and normal brains have different ADC values. High water diffusion in tissue results in a higher ADC value. Recent studies suggest that high-grade gliomas (HGG) exhibit lower ADC values compared to low-grade gliomas (LGG) due to higher tumor cellularity and diffusion restriction in the former. Performing multiple sequences for grading gliomas has a significant economic impact on already strained healthcare systems, making it beneficial to establish a few sequences that better characterize gliomas, both economically and in terms of reduced scanning time. [11] However, there is limited literature and evidence-based data from our region to support ADC findings.

The purpose of our study is to determine the role of mean ADC values in grading gliomas using conventional MRI sequences as the gold standard. We also aim to examine the correlation between ADC values and conventional MRI features of gliomas.

MATERIALS AND METHODS

This was a validation study from September 2022 to December 2023. Its approval for patient data collection was obtained from the institutional review board (Ref: No.886/LRH/MTI, dated 15 August 2022) from MTI, Lady Reading Hospital Peshawar. All patients who were found to have gliomas on MRI were included in the study. Patients who underwent prior treatment, had deficient clinical data, or had inconclusive imaging were excluded from the study.

All patients were referred from OPD and Neurosurgery and neurology wards of LRH to the Radiology department for a brain Scan, and they underwent an MRI scan on a 1.5 Tesla machine (Toshiba Vantage). Imaging sequences included T2-weighted (TR/TE 5160/112 ms), T1-weighted (TR/TE 500/9.4 ms), FLAIR (TR/TE 7000/92 ms, inversion time 2214.1 ms), DWI (TR/TE 4000/97 ms), and gadolinium-enhanced T1-weighted (TR/TE 500/9.4 ms). All images had a 5 mm section thickness, 1 mm intersection gap, and a field of view (FOV) of 23.0 cm × 23.0 cm.

MR imaging results were analyzed using the PACS software. The area of greatest diffusion. Restriction and lowest ADC within the solid component of the tumor were selected, making sure to avoid peritumoral edema. Areas of restricted diffusion within the tumor, appearing as bright signal intensity on DW images and correspondingly low ADC appearing as a dark area on the ADC map, were identified.

The first step in numeric ADC analysis was the examination of T1WI, T2WI, and post-gadolinium sequences to identify and avoid areas likely to be cystic, hemorrhagic, calcific, necrotic, or peri-tumoral edema. Within the remaining areas of the tumor, a section with the lowest visual ADC was identified, and within this section, a spherical Region of Interest (ROI) of 0.16 cm^2 was determined, and the ADC was recorded. In case the low ADC area was large, the ROI was moved slightly, and the means and maximum ADC were determined in the ROI of the lowest ADC. Any difficulties encountered during the selection of the ROI, such as artifacts and hemorrhage, were noted. Following the analysis of T1WI with and without contrast, patterns of enhancement were described as non-enhancing, mild, moderate, and intense.

The study parameters such as gender and age of the patient, lesion location in terms of lobar and superficial or deep location, conventional MRI features such as edema, mass effect, necrosis, and pattern of enhancement, and finally, the mean ADC values were recorded and entered into SPSS 20. The sensitivity and specificity of low ADC for high-grade glioma were calculated along with positive and negative predictive values. The test for normality, i.e., Kolmogorov-Smirnov, shows the normal distribution, so parametric tests, i.e., chi-square test, spearman test, and multiple linear regression, were applied as given in the result.

RESULTS

The study consists of 104 patients, ranging in age from 3 to 87. 59 cases were male, and 45 were female. On cMRI, 62 cases were low-grade glioma, and 42 were high-grade.

The mean ADC for low-grade glioma was 1334.37 ± 300.85 (95% confidence interval for mean of 1257.97 – 1410.77), and for high-grade glioma, it was 842.88 ± 232.013 (95% confidence interval for mean of 770.58 – 915.18). The calculated cut-off value of ADC between the two groups was 1086.58. The sensitivity and specificity of low ADC for high-grade glioma are 83.33 % and 77.42%, respectively. The positive predictive value (PPV) is 71.42 %, and the negative predictive value (NPV) is 87.27%.

There was a significant relationship between ADC cut-off categories and grade of glioma as given in table 1 and chi square test, X^2 (1, N= 104) = 37.089, P < 0.001.

Independent sample T test also established a significant difference of mean ADC among high and low grades glioma as given in table 2.

The lobar distribution of gliomas were as: 33 (31.7%) glioma in frontal lobe (19 LGG – 57%), 25 in parietal (12 LGG – 48%), 13 in temporal (8 LGG – 61%), 6 occipital (5 LGG – 83%), 4 in cerebellum (2 LGG – 50%), 5 in basal ganglia (3 LGG – 60%). 7 in the thalami (3 LGG – 42 %) and 11 in the brainstem (10 LGG – 90%). No significant Correlation was present on Spearman between the Lobar location and grade of glioma, i.e. (rs) [104] = -.123, p = 0.214. No significant correlation was established between glioma type and its location as either cortical or white matter by spearman test, (rs) [104] = -.168, p 0.089. A total of 41 lesions involves the cortex (32 LGG - 78%), while 51 cases were entirely in white matter (27 HGG - 53%) and equal distribution of 6 cases in each grade involving the deep nuclei.

We found only a significant relationship (p <0.001) between Mean ADC and tumor Enhancement, among other characteristics of tumors in multiple linear regression as given in table 3 despite low R^2 = 0.25 of the models. The correlation of ADC cut-off value and enhancement are also given in table 4 with other characteristics of tumor. The relationship of cut off ADC was further explored by chi square test individually with different tumor characteristics on MRI as given in table 5.

Table No 1: Apparent diffusion coefficient vs. Glioma type

ADC value (cut off value of 1086.6 mm2/s)	Glioma type on cMRI		
	High grade	Low grade	Total
Low ADC	35 (71.4 %)	14 (28.6%)	49 (100%)
High ADC	7 (12.7 %)	48 (87.3 %)	55 (100%)
Total	42 (40.4%)	62 (59.6%)	104 (100%)

Table No 2: Independent Sample T-Test for Comparing Mean ADC among grades of glioma with Levene's statistics

ADC Mean Value	Levene's tests for equality of variances		t-test for Equality of Means		
	F	Sig	T	Df	Sig (2 tailed)
Equal variances assumed	3.099	.081	8.935	102	.000
Equal variances not assumed			9.387	100.210	.000

Table No 3: Coefficients of multiple linear regression of ADC and Tumor characteristics

Model 1	Unstandardized Coefficients		Standardized Coefficients	T	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta				Upper Bound
(Constant)	1284.946	55.083		23.328	.000	1175.650	1394.242
Enhancement	-153.426	29.162	-.511	-5.261	.000	-211.289	-95.563
Bleed	117.917	79.268	.138	1.488	.140	-39.369	275.202
Edema	42.423	75.004	.057	.566	.573	-106.401	191.248
Necrosis	-41.397	73.962	-.057	-.560	.577	-188.153	105.359

a. Dependent Variable: ADC Mean Value

Table No 4: ADC vs. Tumor imaging characteristics

ADC (1086.58)	Enhancement				Necrosis		Edema		Bleed	
	No	Mild	Moderate	Intense	None	Yes	No	Yes	No	Yes
Low ADC	10	14	6	19	23	26	17	32	38	11
High ADC	32	11	5	7	33	22	23	32	41	14
Total	42	25	11	26	56	48	40	64	79	25

Table No 5: Relation of ADC cut-off value and tumor characteristics on Chi-Square test:

Tumour characteristics	Chi – Square test (X2)	Degree of Freedom (df)	P-value	Significant?
Enhancement	17.224	3	0.001	Yes
Bleed	0.128	1	0.720	No
Edema	0.556	1	0.456	No
Necrosis	1.778	1	0.182	No

DISCUSSION

The ADC value is a quantitative and, thus, reproducible parameter that has been used to evaluate tumor cellularity to grade gliomas. [12] HGG shows high tumor cellularity, clustering of malignant tissue, and greater curvature of space between malignant cells, leading to slowing down of water molecules giving lower ADC values. [13]

Our study conducted a comprehensive analysis of 104 patients with glioma in which the mean ADC value significantly varied between LGG (1334.37 mm2/s) and HGG (842.88 mm2/s). The calculated cut-off value of ADC (1086.58 mm2/s) effectively distinguished between the two groups.

In the study conducted by Phuttharak et al., [12] it was observed that the ADC values were 969.12 mm^2/s for high-grade gliomas and 1,470.02 mm^2/s for low-grade gliomas. The optimal ADC threshold for distinguishing between tumor grades was determined to be 1119.48 mm^2/s. This threshold yielded a sensitivity of 88.90%, specificity of 90%, positive predictive value (PPV) of 90%, negative predictive value (NPV) of 88.9%, and an overall accuracy of 89.47% in classifying glioma grades.

Differences among the values may be due to differences in ROI size, Magnetic strength, and number of patients. Similarly, the study analysis of pediatric tumors by Yao et al. [14] showed that the cutoff ADC mean value of 1192 mm^2/s for the differentiation between low- and high-grade pediatric gliomas provided a sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of 77.6%, 80.3%, 78.5%, 89.5%, and 62.4%, respectively.

The sensitivity and specificity of ADC values computed by Zhang et al.., based on the currently available data, were 82% and 76%, respectively. This further strengthens the evidence of using ADC for designation grades of glioma. [15]

Guzmán-de-Victoria et al. [16] did a multivariate logistic regression and found that the combination of enhancement and necrosis as independent predictors of tumor grade yielded 95.9% sensitivity and 70% specificity for the differentiation glioma grades.

Apart from tumor enhancement, our study did not find significant correlations between ADC values and other tumor characteristics such as bleeding, edema, and necrosis. While these factors are important in assessing tumor characteristics, the study highlights that ADC is primarily associated with tumor enhancement. Further research may be needed to explore the relationships between ADC and other tumor features in larger cohorts.

Momeni et al. [17] found that the difference between ADC of LGG and HGG is most prominent in the center of the lesion, i.e., 200 mm^2/s, but no significant difference if taken from an oedematous ring or the interface with the normal tissue, i.e., 100 mm^2/s. Our study showed a difference of about ADC mean of 492 mm^2/s, which is taken from the center of the lesion; however, our sample size was double that of their study.

Our study also explored the lobar distribution of gliomas and found no significant correlation between lobar location and glioma grade signifying. This correlates with a study done by Hong et al. [18,]

which also showed no such statistical significance. However, most of the low-grade tumors involve cortical locations. In our study, 31.7% were in the frontal lobe, similar

to the study by Al-Sharydah et al. [19,] which also shows the frontal lobe as the most common location (32.5%).

Our sample size is small, with the potential influence of confounding factors like the inclusion of pediatric and adult patients in the same group, the use of a single scanner, and the broad categorization of tumor grade instead of histological types. Our study did not utilize histopathological grading nor the assessment of proliferative activity by immune markers. Future research should focus on validating these findings in larger cohorts and integrating machine learning approaches for automated glioma classification. This study reinforces that integrating ADC mapping into routine clinical workflows will improve diagnostic accuracy and guide targeted biopsy if needed.

CONCLUSION

The ADC values serve as a non-invasive and reliable radiological marker in distinguishing low- and high-grade gliomas, and improve diagnostic accuracy of conventional MRI and aiding in preoperative decision-making reducing the need of invasive of tissue biopsy, ultimately enhancing patient outcomes.

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Following authors have made substantial contributions to the manuscript as under

Authors	Conceived & designed the analysis	Collected the data	Contributed data or analysis tools	Performed the analysis	Wrote the paper	Other contribution
Khan MI	✓	✓	✓	✓	✓	✓
Khan MZ	✓	✓	×	✓	✓	×
Afzal F	✓	✓	✓	✓	✓	✓
Ahmad FS	✓	✓	✓	×	✓	✓
Zahoor B	✓	✓	×	✓	✓	×
Ishaq BH	✓	✓	×	✓	✓	×

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical Approval:

This Manuscript was approved by the Ethical Review Board of Lady Reading Hospital Peshawar, Vide No. 886/LRH/MTI.

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