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Diffusion Weighted Imaging (DWI) Classification and Apparent Diffusion Coefficient (ADC) Value Tendency Based on Cerebral Glioma Grading in Patients at Dr. Soetomo General Academic Hospital in 2016—2020

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ABSTRACT

Introduction: Glioma grading is crucial to know its prognosis. Magnetic resonance imaging (MRI) is used as a preoperative examination that contains diffusion-weighted imaging (DWI) sequences confirmed by an apparent diffusion coefficient (ADC) value that helps assess tissue based on water diffusion. **Objective:** To prove the relationship between DWI and ADC values with cerebral glioma grading in patients at Dr. Soetomo General Academic Hospital in 2016—2020. **Methods**: This retrospective study collected medical records and MRI files in DICOM (Digital Imaging and Communications in Medicine) format. Gender, age, tumor histopathology, and glioma grading were collected. DWI and ADC values were obtained using the RadiAnt DICOM Viewer application. The data were analyzed using descriptive and analytical statistics. The chi-square test was used to analyze the relationship of DWI with glioma grading, and the spearman rank test was used to analyze the relationship of ADC value with glioma grading. **Results**: The majority of 35 patients were male (54.3%), aged 31–40 years old (22.9%), and the most common histopathology was glioblastoma (37.1%), WHO grade IV. On DWI, most low-grade glioma (LGG) patients showed unrestricted diffusion, and most high-grade glioma (HGG) patients showed restricted diffusion. The ADC value of HGG was lower than the ADC value of LGG. Statistical tests showed a relationship between DWI and glioma grading ($p<0.05$) and a relationship between the ADC value and glioma grading ($p<0.05$). **Conclusion:** There was a relationship between DWI and ADC with glioma grading in Dr. Soetomo General Academic Hospital patients for the period 2016—2020

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INTRODUCTION

Gliomas are the most frequent primary malignant brain tumors in adults.[1] Data from 2009 showed that the incidence of histologically verified glioma patients was 7.3 cases per 100,000 people per year, with glioblastoma being the most common subtype at 71%.[2] Many factors are associated with poor survival in glioma patients, including old age, high tumor grade, multiple lesions, and a low Karnofsky performance score (KPS).[3] One study by Rezaee and Amin Mansour in Iran concluded that the 3-year survival rate in low-grade glioma patients increased after surgery and radiotherapy. In contrast, despite surgery and chemotherapy, the 3-year survival rate of patients with high-grade glioma showed no improvement.[4] Therefore, determining the degree of glioma malignancy in patients is crucial for future prognosis.

Diffusion-weighted imaging (DWI) is an MRI sequence that provides images of tissue microanatomy based on the diffusion motion of proton molecules, which corresponds to Brownian motion.[5] DWI provides images of the tumor microenvironment that conventional MRI sequences cannot depict. DWI can also improve the specificity and sensitivity of conventional MRI images.[6] The use of DWI, especially in the head and neck area, is to look for the presence of primary tumors and nodal metastases, predict and monitor therapy response, and distinguish between residual or recurrent tumors and changes after radiation therapy.[7] The degree to which signal intensity decreases within a given ROI is reflected in ADC values. In other words, ADC can measure changes in signal intensity that occur at different b values of DWI results. These ADC values are obtained pixel by pixel. The minimum, maximum, and average ADC values can be calculated in mm^2/s (square millimeters per second).[8] Different tumors were shown to have various relationships between tumor cell count and ADC. In this case, gliomas, ovarian cancer, and lung cancer have a strong relationship.[9]

At Dr. Soetomo General Academic Hospital, there was no data regarding the relationship between DWI and ADC values with glioma grading. Some researchers have stated that DWI and ADC values can be used to distinguish low- and high-grade gliomas. Phuttharak *et al*. concluded that the visual scale of DWI and ADC values could distinguish high- and low-grade gliomas.[10] High-grade gliomas provide a hyperintensity picture that is not shared by low-grade gliomas. Then, according to a systematic review and meta-analysis by Wang *et al*., the ADC value obtained from DWI has a high degree of accuracy in distinguishing high- and low-grade gliomas.[11] Therefore, DWI and ADC values are believed to have high diagnostic values.

OBJECTIVE

This study aimed to examine the relationship between DWI and ADC values to the grading of cerebral glioma based on histopathology in glioma patients at Dr. Soetomo General Academic Hospital from 2016 to 2020. This data was essential to determine if there were differences from previous studies and was expected to be considered during the MRI examination in evaluating gliomas in the brain so that an accurate diagnosis could be achieved.

METHODS

This retrospective study relied on secondary data to determine the profile of DWI, ADC, and histopathology grading and type. The research protocol has been approved by the Dr. Soetomo General Academic Hospital ethics committees (0771/LOE/301.4.2/I/2022). Research samples derived from patients at the Dr. Soetomo General Academic Hospital in 2016—2020 that match the inclusion criteria.

All subjects had to fulfill the inclusion criteria: cerebral glioma patients with complete and accessible medical records, patients who had undergone MRI examinations, including DWI sequences before treatment, and patients who had histopathology examination results after surgery. Exclusion criteria were patients with residual tumors, patients who died before and during surgery so that the examination results were not recorded in the medical record, patients who underwent a CT scan as a preoperative radiological examination without an MRI examination, and patients with a history of chemotherapy without surgery.

DWIs were obtained with b-values of 0 and 1000 mm^2/s. Then, the images are assessed qualitatively. Tumors with a hypointense appearance on DWI, which is confirmed by high ADC values, are called tumors with unrestricted diffusion. Conversely, tumors that are hyperintense on DWI but have low ADC values are referred to as restricted diffusion. In the cases of hyperintense tumors on DWI that have high ADC values because of the T2 shine-through effect, they are classified as facilitated diffusion. The ADC value was obtained by placing three ROIs in the solid tumor area that experienced changes in signal intensity in DWI using the RadiAnt DICOM Viewer application. Then, the average of the three ADC_{mean} was calculated. Histopathology results and the tumor grading of patients were viewed in the electronic medical record.

The collected data will be analyzed using descriptive statistics to determine the sample's characteristics. In addition to descriptive statistics, the

data would be analyzed analytically using the Chi-square test to examine the relationship between DWI and glioma grading. Then, the Spearman rank test was used to analyze the correlation between the ADC value and glioma grading. The confidence limit was 95% (95% CI) with a significant p-value<0.05. These statistical calculations used SPSS software

RESULTS

This study collected MRI images and histopathology results from 35 glioma patients who met the inclusion and exclusion criteria. Of the 35 patients, 33 had a 1.5 T MRI examination history, and two had a 3 T MRI. In this study, 54.3% of the patients were male, and 45.7% were female. Based on age, the youngest patient in this study was four years old, and the oldest was 63 years old, with an average age of 33.49 years and a standard deviation of 17.828. Most patients were aged 31 to 40 (22.9%). Based on tumor grading and histopathology type, glioblastoma WHO grade IV was the most common glioma (37.1%) compared to other grades and histopathology types.

Most low-grade glioma patients showed unrestricted diffusion on DWI, and only two showed facilitated diffusion. While high-grade glioma patients mostly showed restricted diffusion images on MRI. The chi-square correlation test resulted in a significance value of p=0.026 (p<α, α=0.05) between DWI and glioma grading.

The ADC value of glioma patients in this study ranged from 0.543×10^{-3} mm^2/s to 2.167×10^{-3} mm^2/s. The average ADC value of all glioma patients was $1.165 \pm 0.392 \times 10^{-3}$ mm^2/s. The ADC value of low-grade glioma was in the range of 0.937×10^{-3} mm^2/s to 2.167×10^{-3} mm^2/s with an average of $1.423 \pm 0.400 \times 10^{-3}$ mm^2/s. In comparison, high-grade gliomas were in the range of 0.543×10^{-3} mm^2/s to 1.802×10^{-3} mm^2/s with an average of $1.031 \pm 0.320 \times 10^{-3}$ mm^2/s. The Spearman correlation test between ADC values and glioma grading showed a significance value of 0.002 (p<0.05) and a correlation coefficient of -0.513.

DISCUSSION

Of the 12 LGG patients, six had an unrestricted diffusion DWI picture, four had a restricted diffusion DWI picture, and two had a facilitated diffusion picture. Research by Phuttharak *et al.*, which used a visual scale on DWI, showed different results, namely that most LGG had a weak hyperintense DWI picture (visual scale 4) and fewer isointense and hypointense images (visual scales 2 and 3).[10] This could be due to differences in the proportions of LGG and HGG. In addition, Phuttharak *et al*. did not find facilitated diffusion results on DWI, which could be due to differences in the use of scales where the visual results on DWI were not confirmed in that study by ADC map assessment.[10]

The majority of HGG patients (17 patients) had a restricted diffusion picture, while the remaining 6 HGG patients had an unrestricted diffusion picture. This result is similar to the study of Phuttharak *et al*., where all HGG patients showed hyperintense DWI images with a visual scale of 4 and 5. No LGG patients displayed DWI images with a visual scale of 5, so it can be confirmed that DWI with a visual scale of 5 can distinguish LGG and HGG.[10] Another study also found that a high signal intensity on DWI is helpful in diagnosing the malignant potential of gliomas, and the qualitative evaluation of the D score from DWI properly reflected the pathological grade of gliomas.[12] HGG has characteristics contrary to those of LGG, which is dense and actively growing with a high ratio of nucleus to the cytoplasm and higher intracellular water content than extracellular, so HGG shows high signal intensity on DWI.[13] However, traditional DWI cannot accurately display the actual movement of water molecules since it ignores the effects of capillary microcirculation.[14]

The results of the DWI correlation test with glioma grading produced a significance value of p=0.026 (p<α, α = 0.05), so it was concluded that there was a relationship between DWI and glioma grading in patients at Dr. Soetomo General Academic Hospital for the 2016—2020 period. Similar results were obtained in other research, which found that the visual scale in DWI images can be used to distinguish LGG and HGG. Some previous studies said that increased cellularity, reduced extracellular space, and a high nuclear-cytoplasmic ratio are currently believed to contribute to the limited microscopic water movement in high-grade tumors, resulting in a higher DWI signal intensity than low-grade tumors.[10] Another study discovered that correlating diffusion MR imaging findings with histopathologic findings yielded a more accurate glioma assessment than conventional MRI pre-operative assessment.[15]

The ADC value of LGG, with a range of 0.937×10^{-3} mm^2/s to 2.167×10^{-3} mm^2/s, has an average of $1.423 \pm 0.400 \times 10^{-3}$ mm^2/s. While the ADC value of HGG, with a range of 0.543×10^{-3} mm^2/s to 1.802×10^{-3} mm^2/s, has an average of $1.031 \pm 0.320 \times 10^{-3}$ mm^2/s. Research by Phuttharak *et al*. showed results in the form of an average LGG ADC value of $1{,}396.95 \pm 312.73 \times 10^{-6}$ mm^2/s and an HGG ADC value of $948.31 \pm 148.92 \times 10^{-6}$ mm^2/s. With the median and range of ADC LGG and HGG values, respectively, it is said that the ADC HGG value is significantly lower than the ADC LGG value.[10] Another study found that the ADC_{min} value was significantly lower in the HGG group than in the LGG

group (p<0.0001).[16] In contrast to LGG, the high DWI signal, and relatively low ADC value in HGG cells are because HGG has dense and active growth characteristics with a high nucleus-to-cytoplasm ratio and a higher intracellular water content than extracellular.[13]

The relationship between ADC values and glioma grading in this study resulted in a significance value of 0.002 (p<0.05), which means that there was a relationship between ADC values and glioma grading in patients at Dr. Soetomo General Academic Hospital for the 2016—2020 period. The correlation coefficient in the test was -0.513, so the strength of the relationship between the ADC value and the glioma grading was strongly correlated in a negative direction, which means that the lower the ADC value, the higher the glioma grading. In a study involving 86 samples with brain tumors at Dr. Soetomo General Academic Hospital, researchers also found significant correlations between DWI profiles and ADC values (p=0.000), and between ADC values and tumor histopathology grading (p=0.000).[17] Two meta-analyses in 2017 and 2020 consistently concluded that ADC values provide high accuracy in glioma grading.[11,18] Phuttharak *et al*. found similar results that ADC value can distinguish LGG and HGG. The diagnostic efficacy of the ADC value is better than the DWI visual scale due to the higher AUC on the ADC value.[10] ADC values in the tumor center and edema have better diagnostic values in comparison to the boundary area and normal tissues' ADC values.[19] However, conventional MRI and DWI provide valuable and reliable information and are feasible for grading gliomas in more limited facility conditions and developing countries.[16] Also, ADC parameters derived at high b-values might be more potent in glioma grading than those obtained at standard b values.[20] Moreover, combining DWI with amide proton transfer (APT) and Arterial Spin Labelling (ASL) imaging could improve the ability for glioma grading.[21] High ADC values in LGG may reflect increased interstitial water content. Gliomas with a higher degree of cellularity showed a marked increase in signal intensity on DWI and a significant decrease in ADC values.[16]

This research has some limitations. First, the number of samples with a history of preoperative MRI examination was limited. Many patients reported only having head CT scans without an MRI examination. In addition, some glioma patients' partial or complete DICOM MRI data were unavailable. Some histopathology diagnosis results still need to be upheld.

CONCLUSION

This study found a relationship between DWI and glioma grading in patients at Dr. Soetomo General Academic Hospital for the 2016—2020 period. In addition, there was a relationship between ADC values and glioma grading in patients at Dr. Soetomo General Academic Hospital for the 2016—2020 period.

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Author contributions

The first author conceived and designed the analysis, collected data, conducted data analysis, and wrote the paper. The second author helped to organize and design the analysis and collect data. The third author helped collect data and revised the paper

Conflict of Interest

The authors have no conflicts of interest.

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TABLES AND FIGURES

Table 1. Sample characteristics based on gender and age

Demographics	Frequency (n=35)	Percentage (%)
Gender		
Male	19	54.3%
Female	16	45.7%
Age		
0—10	5	14.3%
11—20	6	17.1%
21—30	3	8.6%
31—40	8	22.9%
41—50	5	14.3%
51—60	7	20%
>60	1	2.9%

Table 2. Sample characteristics based on histopathological type and glioma grading

Grading tumor	Frequency (n=35)	Percentage (%)
WHO grade I		
Pilocytic astrocytoma	6	17.1%
WHO grade II		
Diffuse astrocytoma	3	8.6%
Diffuse infiltrating astrocytoma	1	2.9%
Oligodendroglioma	2	5.7%
WHO grade III		
Anaplastic astrocytoma	5	14.3%
Anaplastic oligodendroglioma	3	8.6%
Anaplastic oligoastrocytoma	2	5.7%
WHO grade IV		
Glioblastoma	13	37.1%

Table 3. DWI characteristics in glioma patients at Dr. Soetomo General Academic Hospital for the period 2016—2020

DWI	Low Grade Glioma	High Grade Glioma
Unrestricted diffusion	6	6
Facilitated diffusion	2	0
Restricted diffusion	4	17

Table 4. ADC value characteristics in glioma patients at Dr. Soetomo General Academic Hospital for the period 2016—2020

Grading	Total	Minimum (10^{-3} mm^2/s)	Maximum (10^{-3} mm^2/s)	Mean (10^{-3} mm^2/s)	SD (10^{-3} mm^2/s)
Low grade glioma	12	0.937	2.167	1.423	0.400
High grade glioma	23	0.543	1.802	1.031	0.320