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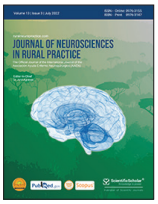

Original Article

Characteristics of isocitrate dehydrogenase-1 status in adult glioma patients: Demographic, radiological, and histopathological insights from single-center study

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ABSTRACT

Objectives: The objective of this study was to determine the characteristic that associated with isocitrate dehydrogenase-1 (IDH-1) status in adult glioma patients.

Materials and Methods: This analytical observational study was conducted on adult glioma patients using a retrospective design. Data were obtained from medical records of patients undergoing treatment at the tertiary general hospital, Dr. Soetomo Hospital, Indonesia, from January 2018 to January 2024. The independent variables included age, gender, tumor location, tumor size, midline shift size, contrast enhancement, and histopathology anatomical grading with IDH-1 status as the dependent variable.

Results: In this study, 21 IDH-1 wild (36.8%) and 36 IDH-1 mutant glioma patients (63.2%) met the inclusion and exclusion criteria. The significant predictors of IDH-1 glioma mutation status ($P < 0.05$) included contrast enhancement, glioma tumor location, and histopathology anatomical grade.

Conclusion: Glioma location, contrast enhancement, and histopathological grading were significantly associated with IDH-1 status in adult glioma patients that potentially be used to predict IDH-1 status in adult glioma patient.

Keywords: Characteristic, Glioma, Isocitrate dehydrogenase-1 mutant, Isocitrate dehydrogenase-1 wild

INTRODUCTION

Glioma is the most common primary brain tumor arising from glial cells, comprising astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas. The 2016 World Health Organization (WHO) classification added immunohistochemistry to the diagnostic criteria, while the 2021 WHO classification further integrated molecular genetic profiling to enable more accurate diagnosis, classification, and prognosis.[1]

Gliomas account for approximately 42.8% of all primary brain tumors, making them the most prevalent intracranial neoplasms.[2] However, limited data are available on the prevalence of isocitrate dehydrogenase-1 (IDH-1) mutations in Asian populations, particularly in Indonesia, as most studies have been conducted in Western populations. In South Asia, IDH-1 mutations in Malaysia were reported in 35% gliomas, while an Indonesian study reported a higher prevalence of 76.1%.[3,4]

IDH is an important enzyme in cellular metabolism, DNA repair, and epigenetic regulation. This enzyme is primarily localized in the cytoplasm and peroxisomes, whereas IDH-2 and IDH-3 are located in mitochondria.[5] There are two types of IDH-1: IDH-1 mutant and IDH-1 wild-type. Clinically, IDH-1 mutant glioma typically occur in younger patients (aged 20–55) and present with seizures, headaches, or behavioral changes.[6] Neuroimaging typically shows IDH-1 mutant gliomas appear more homogeneous, with smaller volumes and less aggressive features, whereas IDH-1 wild-type gliomas tend to be larger, more heterogeneous, and exhibit more aggressive characteristics.[7]

The prognosis of IDH-1 mutation is generally more favorable, due to the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG), which enhances treatment sensitivity and delays tumor progression. In contrast, IDH-1 wild-type gliomas frequently harbor genetic alterations such as telomerase reverse transcriptase (TERT) promoter

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mutations and epidermal growth factor receptor (EGFR) amplification, resulting in more aggressive behavior and reduced therapeutic responsiveness.[4,5]

Despite its prognostic and therapeutic importance, IDH-1 testing in glioma is not routinely performed in many hospitals due to limited resources, lack of diagnostic facilities, and cost constraints. Therefore, this study aimed to analyze the association between clinical demography, radiological, and histopathological features with IDH-1 status in adult glioma patients at Dr. Soetomo General Hospital, a tertiary referral center in Indonesia. Identifying these associated factors may facilitate the prediction of glioma IDH-1 status in centers where immunohistochemical testing was unavailable. By predicting IDH-1 status, clinicians can provide valuable prognostic information for patients who lack access to, or cannot afford, molecular testing.

MATERIALS AND METHODS

A total of 57 glioma patients were enrolled in this study from 2018 to 2024 using a retrospective observational method. These samples were obtained from the medical records at Dr. Soetomo General Academic Hospital, Indonesia. Patient identity, clinical, IDH-1 mutation status, radiology, and central nervous system tumors glioma were obtained according to the WHO 2016 classification. Inclusion criteria were patients with an age of more than 18 years and a diagnosis of glioma based on the medical record. Exclusion criteria were patients with incomplete medical records that did not have information about age, gender, MRI imaging conclusion, and glioma histopathology interpretation.

Data collection

Radiological data regarding glioma location, tumor size, midline shift, and contrast enhancement were assessed by an experienced neuroradiologist and collected from medical records, based on pre-operative magnetic resonance imaging (MRI) examinations. Data regarding glioma pathological anatomy grading and IDH-1 status were obtained from medical records determined by an experienced neuropathologist. The patient tissue slide was stained with hematoxylin-eosin processing and IDH1 R132H reagent to determine IDH-1 mutation status. Figures 1 and 2 show examples of slides tissue processed with IDH1 R132H reagent. High-grade gliomas were defined as WHO grade 3 and 4, while low-grade gliomas were defined as WHO grade 1 and 2, according to the histopathological features of the WHO Classification of Central Nervous System Tumors (2021). The methods were carried out according to the regulations of Dr. Soetomo General Academic Hospital.

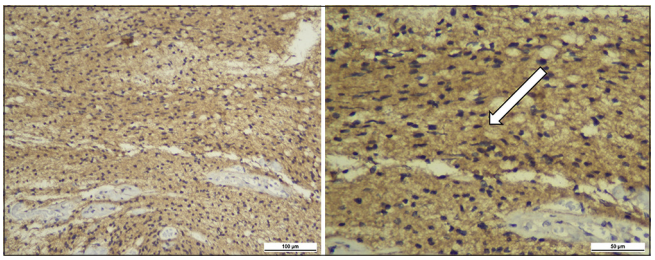

Figure 1: Glioma isocitrate dehydrogenase-1 mutant type using immunohistochemistry (R132H) showed positive stain (white arrow).

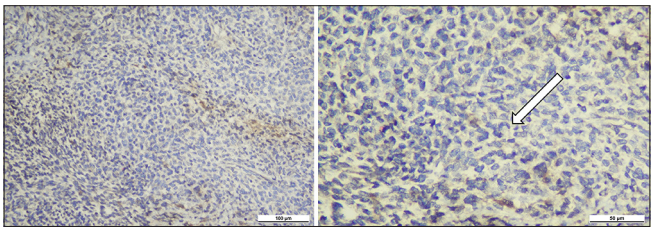

Figure 2: Glioma isocitrate dehydrogenase-1 wild type using immunohistochemistry (R132H) showed negative stain (white arrow).

Statistical analysis

This study compared glioma patients with IDH-1 wild-type and IDH-1 mutant-type. The results comprised categorical variables presented as frequencies and percentages. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22 (IBM SPSS Statistics). Nominal data were analyzed using the Chi-square test (expected cell count ≥5) or Fisher's exact test (expected cell count <5). The Mann–Whitney U-test was applied for non-parametric comparisons of categorical data. Statistical significance was defined as $P < 0.05$ with $\alpha = 0.05$, and the risk factors were presented as odds ratio with 95% confidence interval.

RESULTS

A total 57 glioma patients met the inclusion and exclusion criteria. Table 1 shows the demographic and clinical characteristics of the patients. A total of 21 (36.8%) and 36 (63.2%) patients were classified as IDH-1 wild-type and IDH-1 mutant type. Based on demographic characteristics, IDH-1 wild-type glioma was more frequently observed in patients aged ≥40 years ($n = 12$; 57.1%) and in males ($n = 14$; 66.7%) compared with IDH-1 mutant glioma. However, age and sex did not have a statistically significant association with IDH-1 status ($P > 0.05$) [Table 1].

Based on radiology characteristics, IDH-1 wild-type gliomas were more frequently found in non-frontal location ($n = 19$; 90.5%) with tumor size ≥5 cm ($n = 14$; 66.7%), midline shift >10 mm ($n = 11$; 52.4%), and contrast enhancement ($n = 21$; 100%) compared with IDH-1 mutant-type glioma. However,

Table 1: Glioma patient characteristic.

Characteristic	Total (%)	IDH-1 wild type (%)	IDH-1 mutant type (%)	OR (95% CI)	*P*-value
Number of patients, *n* (%)	57 (100)	21 (36.8)	36 (63.2)		
Age					
≥40 years	30 (52.6)	12 (57.1)	18 (50)	1,333 (0.45–3,94)	0.602[a]
<40 years	27 (47.4)	9 (42.9)	18 (50)		
Gender					
Male	31 (54.4)	14 (66.7)	17 (47.2)	2.235 (0.73–6.841)	0.155[a]
Female	26 (45.6)	7 (33.3)	19 (52.8)		
Location					
Non-frontal	30 (52.6)	19 (90.5)	11 (30.6)	21.591 (4.27–109.15)	0.001[b]
Frontal	27 (47.4)	2 (9.5)	25 (69.4)		
Tumor size					
≥5 cm	35 (61.4)	14 (66.7)	21 (58.3)	1.429 (0.464–4.394)	0.533[a]
<5 cm	22 (38.6)	7 (33.3)	15 (41.7)		
Midlineshift size					
>10 mm	23 (40.4)	11 (52.4)	12 (33.3)		2.651[c]
5–10 mm	20 (35.1)	7 (33.3)	13 (36.1)		
<5 mm	14 (24.6)	3 (14.3)	11 (30.6)		
Contrast enhancement					
Yes	41 (73.7)	21 (100)	20 (71.9)		0.000[b]
No	15 (26.3)	0 (0)	16 (28.1)		
Histopatological grading					
High grade	42 (73.7)	21 (100)	21 (58.3)		0.001[b]
Low grade	15 (26.3)	0 (0)	15 (41.7)		

[a]Chi square, [b]Fisher exact test (expected cell count <5), [c]Mann–Whitney test. OR: Odd ratio, CI: Confidence interval, IDH-1: Isocitrate dehydrogenase-1. *P*-value (< 0.05).

only location and contrast enhancement had statistically significant associations with IDH-1 status ($P < 0.05$). Glioma with IDH-1 wild type was frequently reported in high grade ($n = 21$; 100%) compared to IDH-1 mutant-type ($P < 0.05$) [Table 1].

Based on histopathology characteristic, glioma with IDH-1 wild type was more frequently found in high grade ($n = 21$; 100%) compared with IDH-1 mutant-type that has statistic significant in our study ($P < 0.05$) [Table 1].

Tumor location, contrast enhancement, and histopathological grading were statistically significant with glioma IDH-1 status ($P < 0.05$). Other variables such as age, sex, tumor size, and midline shift size did not have statistical significance with IDH-1 status ($P > 0.05$) [Table 1].

DISCUSSION

The determination of IDH-1 status in glioma represents the first step in the 2021 WHO classification, serving as both a major prognostic marker and therapeutic target.[1] Although IDH-1 testing has become routine in other developed countries, its implementation in Indonesia remains limited. Consequently, epidemiological studies assessing IDH-1 status are essential to improve understanding of the clinicopathological and radiological characteristics of glioma.

The prevalence of IDH-1 mutation in gliomas varies considerably across regions. In Asian populations, reported IDH-1 mutant frequencies range from 53.7% in Korea, 56.8% in India, and 40.6% in China. In our study, based on an Indonesian population, 63.2% of glioma cases were identified as IDH-1 mutant type. In contrast, studies from Western countries, such as research from England, reported an IDH-1 mutant prevalence of only 19.5%, and data from the Central Brain Tumor Registry of the United States indicated that IDH-1 wild-type gliomas have a higher incidence among glioma adult patients. These findings suggest that Asian populations may have a higher incidence of IDH-1 mutant gliomas compared with Western populations. Such heterogenicity likely reflects population-specific genetic and environmental factors, which need further investigation.[8-12]

The role of gender in predicting IDH-1 status remains controversial. Some studies have suggested that estrogen

exerts a protective effect against gliomagenesis, resulting in a lower incidence of IDH-1 wild-type gliomas among women.[13] However, our findings, along with those from other Indonesian studies, found no significant sex-related differences between IDH-1 mutant and IDH-1 wild-type gliomas, suggesting that hormonal influence may not be a decisive factor.[6,14]

In our study, there was no significant difference in IDH-1 status between older (≥40 years) and younger patients (<40 years). Previous meta-analyses identified age as a predictor factor for IDH-1 wild-type gliomas diagnosed in older patients (median 68–70 years) compared with IDH-1 mutant gliomas (median 45–48 years).[15] This pattern has been associated with age-related accumulation of genetic alterations such as TERT promoter mutations, EGFR amplification, and phosphatase and tensin homolog (PTEN) loss. This inconsistency between our findings and prior study may be due to variations in lifestyle and environmental exposures across different populations.[16,17]

Based on histopathological findings, our study, along with previous reports, demonstrated a significant difference that reinforce the established correlation between histopathological grading with IDH-1 status in glioma.[14,18] IDH-1 mutant glioma is more frequently observed in low-grade tumors (WHO grade II), characterized by monomorphic cells, infiltrative margins, low mitotic activity, and absence of necrosis. In contrast, IDH-1 wild-type glioma is predominantly found in high-grade tumors (WHO grade III-IV), which exhibit marked pleomorphism, high mitotic rate, microvascular proliferation, and pseudopalisading necrosis.[19] These differences are consistent with the biological effects of the oncometabolite 2-HG, which induces global DNA hypermethylation (Glioma-CpG Island methylator phenotype) and decreases proliferative capacity in IDH-1 mutant glioma.[20]

Tumor location is one of the important predictive factors for IDH-1 status. Our results show that IDH-1 mutant gliomas are predominantly located in the frontal lobe. This predilection may be explained by regional differences in progenitor cell susceptibility and metabolic environment. The frontal cortex exhibits higher glutamatergic activity and increased glutamate dehydrogenase 2 expression, which may facilitate the growth of IDH-1 mutant gliomas.[21,22] In addition, frontal lobe glioma is more susceptible to gross total resection, which contributes to the improved prognosis associated with IDH-1 mutant gliomas.[23,24]

Imaging evidence supports that IDH-1 wild-type gliomas exhibit significantly greater contrast enhancement, reflecting hypervascularity and blood-brain barrier disruption. Accumulation of contrast agent within areas of abnormal neovascularization produces the characteristic thick and heterogeneous enhancement. This radiographic pattern likely reflects upregulated vascular endothelial growth factor (VEGF) signaling and pro-inflammatory mediators, which increase microvascular density and permeability, resulting in more intense contrast enhancement compared to typical IDH-1 mutant glioma.[25,26]

IDH-1 wild-type gliomas tend to exhibit faster growth, larger tumor size, and more extensive peritumoral edema. Upregulated VEGF and pro-inflammatory cytokines (Tumor necrosis factor-alpha, interleukin [IL]-6, and IL-1β) increase vascular permeability and drive angiogenesis, thereby amplifying edema, mass effect, and midline shift. Consequently, compared with IDH-1–mutant gliomas, IDH-1-wild-type tumors more often present with greater mass effect. Nevertheless, prior studies and this study have shown statistically not significant differences in tumor size or midline shift between IDH-1 groups. This inconsistency may be due to the limitations of our study, as we analyzed tumor size at a single time point without growth-rate estimates and did not measure lesion-to-midline distance. These factors may account for the absence of statistical significance in both tumor size and midline shift.[26,27]

Strength and limitations of the study

This study focuses on the characteristics of IDH-1 mutations in a Southeast Asian population, specifically in Indonesia, where limited research has been conducted. This is valuable given the known ethnic and regional variations in glioma. However, this study has several limitations that should be acknowledged. First, the relatively small sample size may limit the statistical power and generalizability of the findings. Second, the retrospective design, which relied on medical records, may introduce potential biases, including incomplete data and variability in imaging or pathological interpretation. Third, the use of IDH1 R132H immunohistochemistry as the sole molecular diagnostic tool may have missed non-R132H IDH1 or IDH2 mutations, leading to possible misclassification of some cases. Nevertheless, IDH1 R132H immunohistochemistry remains a reliable, practical, and widely adopted neuropathological diagnostic method used globally for the detection of IDH-1 mutation in gliomas.[28]

Future research is needed to determine other variables used to predict IDH-1 status in glioma patients, multi-center studies with larger cohort study, and incorporation of next-generation sequencing for comprehensive IDH1/2 profiling.

CONCLUSION

Tumor location, contrast enhancement, and histopathological grading were used to predict IDH-1 status in glioma. IDH-1 mutant-type was the most frequent subtype among glioma patients at Dr. Soetomo General Hospital, Indonesia. Histopathological analysis revealed that low-grade glioma

were predominantly IDH-1 mutant, while high-grade glioma were predominantly IDH-1 wild-type. Tumor location was a statistically significant predictor of IDH-1 status in glioma. IDH-1 mutant and IDH-1 wild type were reported in the frontal and non-frontal lobes, respectively.

IDH-1 molecular testing remained the gold standard and was performed following the availability of resources and expertise, even though clinical demographic, radiological, and histopathological features were associated with IDH-1 status.

Ethical approval: The research/study approved by the Institutional Review Board at Dr. Soetomo General Hospital, approval number 1114/KEPK/X/2024, dated 7th October 2024.
Declaration of patient consent: Patient's consent was not required as there are no patients in this study.
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Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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