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ORIGINAL ARTICLE

Clinicopathological Characteristics of Diffuse Gliomas According to IDH1 Mutation Status

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ABSTRACT

Background: *Diffuse gliomas are the most common primary malignant tumors of the central nervous system and exhibit marked clinical, histopathological, and molecular heterogeneity. Isocitrate dehydrogenase 1 (IDH1) mutation is a key molecular marker incorporated into the World Health Organization classification of diffuse gliomas because of its diagnostic and prognostic significance. Characterizing the clinicopathological features according to IDH1 mutation status may improve disease stratification and optimize patient management.* ***Objective:*** *To evaluate the clinicopathological characteristics of diffuse gliomas according to IDH1 mutation status.* ***Materials & Methods:*** *This cross-sectional analytical study included 110 consecutive patients with histopathologically confirmed diffuse glioma who underwent surgical resection at the Department of Neurosurgery, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh, between July 2020 and December 2021. IDH1 mutation status was determined by immunohistochemistry. Demographic characteristics, clinical presentation, histopathological subtype, WHO grade, and radiological findings were recorded using a structured data collection form. Statistical analyses were performed using SPSS version 26, and a p-value <0.05 was considered statistically significant.* ***Results:*** *The mean age of the participants was 40.75 ± 15.68 years, and 60.0% were male. Astrocytoma was the predominant histological subtype (88.2%), while WHO grade IV tumors constituted 49.1% of cases. IDH1 mutation was detected in 93 (84.5%) patients. Patients with IDH1-mutant gliomas were younger than those with IDH1-wild-type tumors (39.6 vs. 47.1 years). IDH1-mutant tumors were more frequently associated with frontal lobe involvement and favorable clinicopathological characteristics than IDH1-wild-type tumors.* ***Conclusion:*** *IDH1 mutation was highly prevalent among patients with diffuse glioma and was associated with distinct clinicopathological characteristics. Incorporating IDH1 mutation status into routine evaluation may enhance the classification and clinical assessment of diffuse gliomas.*

Keywords: *Diffuse glioma, IDH1 mutation, Astrocytoma, WHO grade, Immunohistochemistry*

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INTRODUCTION

Diffuse gliomas are the most prevalent primary malignant tumors of the central nervous system (CNS), comprising roughly 30% of all primary brain tumors and around 80% of malignant brain neoplasms. These tumors represent a heterogeneous group of neoplasms with diverse histopathological, molecular, and clinical characteristics that strongly influence prognosis and therapeutic response [1]. Diffuse gliomas remain a significant cause of morbidity and mortality as a result of their infiltrative nature and biological heterogeneity in the face of advances in neurosurgery, neuroimaging, and adjuvant therapies [2]. There has been a major paradigm shift in the classification of diffuse gliomas over the last decade. Gliomas were traditionally only classified based on histopathological features, but the recent updates to the World Health Organization (WHO) classification that include molecular biomarkers have increased both diagnostic accuracy and prognostic stratification. The integration of molecular alterations with histopathological findings, among which are mutations in the IDH1 gene, became standard based on the 2021 WHO Classification of Tumors of the Central Nervous System [3], as mutations in the IDH1 gene are one of the most important biomarkers for diffuse gliomas. Such an approach offers increased accuracy of glioma diagnosis accompanied by a more tailored treatment plan.

IDH1 acts as a cytosolic metabolic enzyme converting isocitrate to α-ketoglutarate. The mutation in IDH1 provides D-2-hydroxyglutarate, an oncometabolite responsible for epigenetic modifications, impaired cell differentiation, and gliomagenesis [4]. Compared with IDH1-wild-type tumors,

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IDH1-mutant diffuse gliomas occur more frequently in younger patients, are generally less biologically aggressive, and have prolonged overall survival [5]. Thus, IDH1 mutation status determination is now an integral part of the usual pathological assessment of diffuse gliomas. In addition to prognosis, IDH1 mutation status has been correlated with several clinicopathological characteristics. Although patients with IDH1 mutant gliomas tend to be younger and have lower-grade tumors than patients with IDH1 wild-type gliomas, whether the presence of any of these mutations correlates with the age at diagnosis is less clear [6]. They are also associated with inter-subtype histological heterogeneity, clinical variability, and imaging properties variation, suggesting that molecular alterations can affect the biology of diffuse gliomas and their clinical aspect [7]. The establishment of these clinicopathological unique characteristics is important for more accurate risk stratification, optimal treatment planning, and prognosis.

The association between IDH1 mutation status and clinicopathological characteristics has been found in several studies from Europe, North America, and East Asia in IDH1 mutated diffuse gliomas [8,9]. In contrast, the evidence from South Asian countries, especially Bangladesh, is scarce. Possible variation in socio–demographic characteristics, tumor biology, access to healthcare, and genetic background may modify the clinicopathological profile of gliomas in this region. Thus, local data on IDH1 mutation and its association with clinicopathological characteristics among Bangladeshi patients need to be elucidated.

The current study was conducted in order to assess the clinico-pathological profiles of gliomas according to IDH1 status in a cohort of patients treated by surgery in a tertiary neuroscience institute in Bangladesh. The results of this study will help provide insight into the demographic, clinical, and histopathological profile of diffuse gliomas as well as improve molecular classification and evidence-based management of these tumors in everyday clinical practice.

MATERIALS & METHODS

This cross-sectional observational study was carried out at the Department of Neurosurgery, National Institute of Neurosciences and Hospital (NINS&H), Dhaka, Bangladesh. The study was conducted over 18 months from July 2020 to December 2021. A purposive consecutive sampling method was conducted to recruit 110 consecutive eligible patients. The final analysis only included patients with histopathologic ally confirmed diffuse gliomas and IDH1 mutation status available via immunohistochemical evaluation.

Inclusion Criteria

All patients regardless of age or gender with clinical and radiological signs of intracranial diffuse glioma. Histopathological diagnosis corresponding to diffuse glioma subtype on pathology (astrocytoma, oligodendroglioma, or mixed oligoastrocytoma). Availability of immunohistochemical assessment for IDH1 mutation status.

Exclusion Criteria

Patients who refused to participate in study. Histopathological findings inconsistent with glioma. Patients with recurrent glioma or who had previous received radiotherapy and/or chemotherapy.

Data Collection Procedure

Eligible patients were recruited after giving a written informed consent. A structured form for data collection was used to collect demographic, clinical, neurologic examination and computed tomography findings. Tumour location was determined by review of pre-operative magnetic resonance imaging (MRI). Tumor tissues were collected after surgical resection, and were subjected to histopathological examination and immunohistochemical identification of IDH1 mutation status. Histopathological subtype and WHO grade was recorded for each patient.

Study Variables

IDH1 mutation status (mutant versus wild type) was the primary outcome variable. Independent variables included age, sex, clinical mold, location of the tumor, histopathological subtype and WHO-grade.

Statistical Analysis

Data were entered, cleaned, and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between IDH1-mutant and IDH1-wild-type gliomas were performed using the Chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. A two-tailed p-value of <0.05 was considered statistically significant.

Ethical Considerations

Ethical approval was obtained from the Ethical Review Committee (ERC) of the National Institute of Neurosciences and Hospital (NINS&H), Dhaka, Bangladesh, before commencement of the study. Written informed consent was obtained from all participants or their legal guardians prior to enrollment. Participant confidentiality and anonymity were maintained throughout the study, and all procedures were conducted in accordance with the ethical principles of biomedical research.

RESULTS

Presents the age distribution of study participants. The average age of the patients at the time of surgery was 40.75 ± 15.68 years (range from 1 to 70 years). The 30–49 years age group accounted for almost half of the study population (48.1%), showing that diffuse gliomas mainly occurred in middle-aged individuals in this cohort. Only 9.1% of the study population was less than 20 years old, while 29.0% of patients were at least 50 years old (*Table I*).

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Table I: Age distribution of the study participants (*n* = 110)

Age group (years)	Number (n)	Percentage (%)
0–9	3	2.7
10–19	7	6.4
20–29	13	11.8
30–39	26	23.6
40–49	27	24.5
50–59	16	14.5
60–69	16	14.5
70–79	2	1.8
Total	110	100.0
Mean ± SD (years)	40.75 ± 15.68	
Range (years)	1–70	

The most common presenting symptom was headache in 98 (89.1%) patients followed by seizure in 75 (68.2%) patients. Thirtysix (32.7%) patients had vomiting and 33 (30.0%) had weakness of any part of the body. Visual disturbance and altered consciousness were less common, presenting in 16.4% and 11.8% of patients. Due to the number of symptoms recorded in patients, the total percentage goes above 100% (*Table II*).

Table II: Clinical presentation of the study participants (*n* = 110)

Clinical presentation*	Number (n)	Percentage (%)
Headache	98	89.1
Seizure	75	68.2
Vomiting	36	32.7
Weakness of any part	33	30.0
Blurring of vision	18	16.4
Altered consciousness	13	11.8
Others	13	11.8

Overall anatomical distribution of diffuse gliomas as seen on preoperative neuroimaging. Forty-two tumors (40.0%) were located in the frontal lobe followed by 52 (47.3%) in the parietal lobe and 20 (20.0%) in the temporal lobe. Occipital and insular lobe involvement was not common. Reference group (non-survival) Tumors located in other anatomical sites: Thalamus, corpus callosum, posterior fossa and brainstem were 9.1% of cases. As some tumours extended into neighboring lobes, the cumulative percentages summed to above 100% (*Table III*).

Table III: Anatomical distribution of tumor location (*n* = 110)

Tumor location	Number (n)	Percentage (%)
Frontal lobe	52	47.3
Parietal lobe	44	40.0
Temporal lobe	22	20.0
Other locations	10	9.1
Occipital lobe	4	3.6
Insular lobe	3	2.7

Histopathological features of the study participants are summarized in Table 4. Astrocytoma, the most common histological subtype, represented 97 (88.2%) of all diffuse gliomas. Oligodendroglioma was diagnosed in 11 (10.0%) patients and mixed oligoastrocytoma in 2 (1.8%) cases. The current study was therefore able to demonstrate that astrocytic tumors made up the vast majority of all surgically treated diffuse gliomas (*Table IV*).

Table IV: Histopathological subtype of diffuse gliomas (*n* = 110)

Histopathological subtype	Number (n)	Percentage (%)
Astrocytoma	97	88.2
Oligodendroglioma	11	10.0
Mixed oligoastrocytoma	2	1.8
Total	110	100.0

Table V summarizes the distribution of WHO grades and IDH1 muta-tion status. As per WHO classification, the majority of the tumors were observed to be of Grade IV gliomas (49.1%) followed by Grade II (40.9%) and Grade III (10.0%) tumors. By immunohistochemical analysis91 (84.5%) patients had IDH1-mutant tumors and 17 (15.5%) had IDH1-wild-type tumors. We observed a high proportion of IDH1 mutation among diffuse glioma patients included in this study (*Table V*).

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Table V: Distribution of WHO grade and IDH1 mutation status (*n* = 110)

WHO grade	Number (n)	Percentage (%)
Grade II	45	40.9
Grade III	11	10.0
Grade IV	54	49.1
Total	110	100.0
IDH1 status		
IDH1 mutant	93	84.5
IDH1 wild type	17	15.5
Total	110	100.0

Age according to IDH1 mutation status is shown in Table 6 IDH1-mutant diffuse gliomas developed at a younger mean age (39.60 years) compared with IDH1-wild-type tumors (47.06 years). Although IDH1-mutant tumors tended to occur more frequently in elderly patients, one-way ANOVA did not detect a statistically difference in age 3 per IDH1 mutation status (p = 0.071). Previous studies have indicated a possibility of age-onset bias towards younger age for IDH1/2-mutant diffuse gliomas without a statistically significant association in the current cohort (*Table VI*).

Table VI: Comparison of age according to IDH1 mutation status (*n* = 110)

IDH1 mutation status	Mean age (years)	Number (n)	p-value
IDH1 mutant	39.60	93	
IDH1 wild type	47.06	17	0.071
Overall	40.75	110	

DISCUSSION

This study assessed the profile of diffuse gliomas in relation to IDH1 mutation status in patients from a tertiary neuroscience center in Bangladesh. Results: This study concluded that diffuse gliomas typically occurred in middle-aged adults, exhibited clear male predominance, and that a headache was frequently the first presenting symptom. In addition, the frontal lobe was the most frequently affected anatomic location. Our results are largely in accordance with the previous reports in which certain discrepancies were noted regarding the patient demographics as well as molecular characteristics.

The study population was primarily 40.75 ± 15.68 years of age, and almost half of the patients were between the ages of 30 and 49 years old. This finding indicates that most of these diffuse gliomas in the current cohort belonged to adults with mentally disordered kleptomania. We observed similar findings in Krishnatreya et al and Mukherjee et al, who noted that diffuse gliomas in the South Asian population tend to occur at a younger age compared to those in Western countries [10,11]. The difference in age observed by the current study may be a reflection of demographic variations, population structure, healthcare-seeking behavior, referral patterns, and population genetics. This epidemiological pattern can also be partly attributed to the relatively young national population of Bangladesh. In the present study sample, male predominance was observed with a male-to-female ratio of nearly 1.5:1. This result is consistent with our reports by Ostrom et al and Rasmussen et al [2,8]. and others consistently show a higher prevalence of diffuse gliomas amongst males. However, the biological basis of this sexual dimorphism is not yet completely understood, and factors such as hormonal influences, environmental exposures, and sex-specific genetic susceptibility have been postulated.

In terms of clinical presentation, headache was the most frequent symptom (89.1%), followed by seizure (68.2%), vomiting (32.7%), and motor weakness (30.0%). Headaches and seizures, as the most common presenting features of diffuse gliomas [12]. Likewise, Bai et al, showed that for large tumors, neurological deficits are dependent on size, location, and associated cerebral edema [7]. The prevalence of headache in the current study may be high, likely due to raised intracranial pressure secondary to relatively large or high-grade tumors, especially, while a high rate of seizures may reflect involvement of the cortex in these patients, particularly in frontal and temporal regions.

The anatomical distribution of tumors showed that the most common site was the frontal lobe (47,3%), followed by the parietal (40,0%) and temporal (20,0%) lobes. This observation corresponds to the studies from Wang et al and Yu et al, and both found that diffuse gliomas, especially IDH1 mutant diffuse gliomas, most often originate from the frontal lobe [13,14]. Similarly, Sonoda et al. In their meta-analysis, reported that molecularly attractive gliomas frequently occur in the frontal region more than other cerebral locations [9]. The relative abundance of frontal lobe tumors may derive from location-specific features of glial cell spectrum, molecular variability, and tumor biology.

As one of the three major subtypes of diffuse glioma, astrocytoma composed 88.2% of the histologic diagnoses in the current study; only a minority of cases were oligodendroglioma and mixed oligoastrocytoma. This observation is consistent with the finding of Mukherjee et al, which showed astrocytoma to be the most common histological subtype in patients with diffuse glioma [11]. Similarly, Rasmussen et al demonstrated that astrocytic tumors constituted most adult diffuse gliomas recorded in the Danish Neuro-Oncology Registry [8]. The relatively high percentage of astrocytoma in the current cohort may represent the reality of the increasing availability of astrocytic neoplasms, referral bias to a tertiary neurosurgical center, and the focus including equally both or soever from surgically treated patients. For tumor grade, the greater percentage of WHO grade IV gliomas was 49.1%, whereas WHO grades II and III were both low (40.9 and 10.0%). Annexin V combined with ACTE and PACT as a target for sustained release of therapeutic LE different from tumorigenic physiological 1, where glioblastoma is the most frequent deadly form of certain kinds of malignant primary brain tumor found. Likewise, Louis et al. High-grade diffuse gliomas have, however, remained the prevalent subtype encountered by practitioners in real-life clinical settings [3]. The significant number of grade IV tumors in this study may well be in part due to delay in presentation,

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relatively high referral of advanced cases to specialist neurosurgical centers, and aggressiveness of diffuse gliomas.
Overall, the results of this study are broadly in line with contemporary literature and emphasize the integration of molecular biomarkers with traditional histopathological assessment. Introduction of IDH1 mutation status into standard diagnostic practice enhances tumor classification, prognostic stratification, and personalized therapeutic decision-making in alignment with the 2021 WHO Classification of Central Nervous System Tumors. Our current findings also provide important baseline data on this pathology in Bangladesh, where the molecular characterization of diffuse gliomas to date has been minimal.

CONCLUSION

All diffuse gliomas were predominantly seen in adult males, with astrocytomas being the most common histopathological subtype. The largest fraction of cases was contributed by WHO grade IV tumors, and IDH1 mutation was present in a large majority of the patients. Patients with IDH1-mutant gliomas were younger than those with IDH1-wild-type tumors, revealing the heterogeneity of diffuse gliomas. Collectively, these results underscore the increasing importance of merging molecular markers with standard histopathological diagnosis to achieve accurate tumor categorization and refined risk stratification. Routine testing of IDH1 mutation status may help obtain more accurate diagnoses, prognosis, and personalized therapy. These findings should be confirmed through larger healthcare system-based multicenter studies and comprehensive molecular profiling in other adjacent western regions of Bangladesh to improve the management of diffuse gliomas here.

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CONFLICT OF INTEREST

None declared

ETHICAL CONSIDERATION

The study was approved by ethical review committee.

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