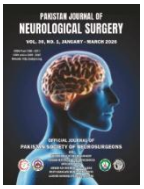

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Original Research

Incidence and Outcomes of High-Grade Gliomas in Young Adults: An Emerging Challenge

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ABSTRACT

Objective: High-grade gliomas are typically associated with older age, whereas low-grade gliomas are more common in young people. However, in recent years, there has been a surge in high-grade gliomas among the young population in our area, which prompted us to examine this phenomenon more closely and its implications for treatment. To measure the incidence of high-grade gliomas in the young population and to examine trends. In addition, we examined the molecular characteristics of these gliomas and the postoperative outcomes following resection.

Materials & Methods: A retrospective study was conducted in our department, in which we reviewed patient records from January 2022 to July 2025. We included 85 patients in our final cohort aged 18 to 39 years with a confirmed diagnosis of high-grade glioma (WHO Grades III and IV). Our exclusion criteria were individuals with low-grade gliomas, non-glial tumors, or incomplete records. From available patient records, we extracted demographic data, tumor incidence, molecular markers (IDH, MGMT, ATRX), and clinical outcomes. Statistical analysis was done on SPSS version 26.

Results: Results showed a statistically significant increase in the incidence of high-grade gliomas in young adults ($p < 0.01$). Molecular analysis revealed that IDH-wildtype tumors accounted for 74% (37 of 50 cases). Of these, 43.2% exhibited MGMT promoter methylation (16 of 37). Among the IDH-mutant cases (26%, 13 of 50), ATRX loss was present in 84.6% (11 of 13 cases). The median overall survival was 16.5 months.

Keywords: High-Grade Glioma, Young Adults, Molecular Profiling.

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INTRODUCTION

High-grade Gliomas (HGGs), defined as WHO

grades III and IV are more commonly associated with older populations, whereas younger populations are relatively spared and affected primarily by low-grade Gliomas.[1,2] In recent years, however, there has been an increase in the incidence of High-grade Gliomas in young adults, particularly between ages 18 and 39, underscoring the need to study these tumors in this population and their outcomes.[3] There is a stark difference in the symptoms and molecular features of these tumors compared with those of older adults, creating an additional layer of complexity. Despite the upward trend, there is a lack of regional data on treatment trends and their implications. Ongoing research indicates that HGGs in young adults are not simply the same disease as in older patients. They are biologically distinct. The behavior of these tumors is largely driven by molecular alterations in genes crucial for cancer progression, namely MGMT promoter methylation and isocitrate dehydrogenase (IDH).[4,5] While it is generally true that IDH-mutant tumors are more common in younger patients, a significant number of young adults with HGGs have IDH-wildtype tumors, which are more aggressive and associated with poorer outcomes.[6,7] In addition, tumor survival rates vary with demographic parameters, the impact of which is not yet fully understood. These uncertainties raise important questions about whether current treatment strategies are appropriate for young adults with HGGs.[8,9]

While it has been noticed that high-grade glioma cases are increasingly coming up in young adults, there has been a lack of knowledge regarding the behavior of high-grade glioma in this particular age group. The major aim of this study has been to bridge this knowledge gap by undertaking the investigation of the tumor incidence, molecular profile, and outcomes of the treatment. By undertaking the study through the investigation of this patient population, the research has aimed to identify the trends that could further help to make precise estimations of both the prognosis and treatment of high-grade glioma in this category of young patients.[10] While undertaking this study by placing particular emphasis on the molecular markers of this tumor, this research has sought to further identify how high-grade glioma differs in young adults from low-grade glioma cases and how it differs in this category of people from the cases of high-grade glioma that occur in older adults.

METHODS AND MATERIALS

Study Design

A retrospective study was conducted at the Department of Neurosurgery, Punjab Institute of Neurosciences (PINS), between January 2022 and July 2025. The study was approved by the Institutional Review Board (IRB) department of PINS. Because the study screened only existing records, the need for informed consent was waived.

Participants

A non-probability convenience sampling method was employed, in which we included 85 patients with high-grade gliomas of WHO grades III and IV after reviewing their medical records.

Materials and Data Collection

Each case was histopathologically confirmed as intracranial HGG. Our exclusion criteria included patients with low-grade gliomas, non-glial tumors, or incomplete records to ensure reliable data. We extracted demographic and clinical data from hospital records, including age, gender, tumor location, and surgical outcomes. Detailed treatment parameters, including radiotherapy dose, number of temozolomide cycles, and treatment adherence, were not uniformly available in retrospective records and were therefore not included in quantitative analysis. Patients were managed according to institutional protocols whenever feasible.

Data Analysis

For the molecular workup, we looked at the main biomarkers commonly used in glioma evaluation, including IDH mutation status, MGMT promoter methylation, and ATRX expression. These markers were analyzed by immunohistochemistry and molecular genetic methods to ensure accurate tumor classification. Molecular profiling was available for 50 of 85 patients (58.8%). Testing was performed when adequate tumor tissue and laboratory resources were available. Patients without molecular testing were retained in overall clinical analyses; however, subgroup analyses involving molecular markers were restricted to cases with available data.

Surgical outcomes were assessed primarily by median overall survival, and postoperative complications, such as new neurological deficits or tumor recurrence, were also recorded.

Where available, the extent of tumor resection was classified from operative records and early postoperative imaging as gross total resection (GTR), subtotal resection (STR), or biopsy only. Among the 85 patients, gross total resection was achieved in 36 (42.4%), subtotal resection in 29 (34.1%), and biopsy alone in 20 (23.5%). Biopsy-only procedures were primarily performed for deeply located tumors, including brainstem lesions or tumors adherent to eloquent structures, where safe resection was not feasible. Several of these cases demonstrated highly aggressive histological features, including rare teratoid/rhabdoid morphology.

All statistical analyses were carried out using SPSS version 26.0. Descriptive statistics were used to outline patient demographics and tumor characteristics. Categorical variables included in the results were reported as percentages. To study changes in yearly incidence, the Cochran–Armitage trend test was applied, with $p < 0.05$ considered statistically significant. Overall survival across different molecular groups was compared using Kaplan–Meier survival curves. The study was conducted in accordance with ethical guidelines and standard practices in clinical oncology research.

RESULTS

Patient Demographics and Tumor Grade

We analyzed 85 young adults aged between 18 and 39 years who were diagnosed with high-grade gliomas during the study period. Among them, 50 patients (59%) had WHO Grade IV gliomas, while 35 patients (41%) had WHO Grade III gliomas.

Extent of Resection

Gross total resection was achieved in 36 patients (42.4%), subtotal resection in 29 patients (34.1%), and biopsy only in 20 patients (23.5%). Biopsy-only cases were predominantly deep-seated tumors involving the brainstem or critical functional regions. Among biopsy-only tumors, 7 cases demonstrated highly aggressive histological variants with teratoid/rhabdoid features.

Postoperative Neurological Outcomes

Postoperative neurological deficits were documented in clinical records; however, reporting was inconsistent, and standardized complication rates could not be reliably calculated. Formal statistical analysis of postoperative morbidity was therefore not performed.

Incidence Trends

The annual number of new cases showed a statistically significant increase in incidence, as indicated by the Cochran-Armitage test ($p < 0.01$).

Molecular Characteristics

Molecular data were available for 50 patients. The majority (74%, 37 patients) had IDH wild-type status (Figure 1). Among these, MGMT promoter methylation was present in 43% of tumors (16 cases) (Figure 2). IDH mutations were identified in

13 patients (26% of those with molecular data). Loss of ATRX expression was noted in 85% (11 out of 13) of the IDH-mutant tumors.

Survival Outcomes

The median overall survival for all patients was 16.5 months (95% CI, 13.2–20.1). Survival outcomes were not analyzed separately for IDH-mutant and IDH-wildtype subgroups due to limited sample size and incomplete follow-up data within molecularly characterized patients.

Table 1: *Clinicopathological Characteristics and Molecular Profile of Young Adult Patients with High-Grade Gliomas (n = 85).*

Variable	Category	n (%)
Age group (years)	18–39	85 (100)
WHO tumor grade	Grade III	35 (41.2)
	Grade IV	50 (58.8)
Extent of resection	Gross-total resection	36 (42.4%)
	Sub-total resection	29 (34.1%)
	Biopsy	20 (23.5%)
Trend in annual incidence	Increasing trend	$p < 0.01$†
Molecular profiling available	Yes	50 (58.8)
IDH mutation status (n = 50)	IDH-wildtype	37 (74.0)
	IDH-mutant	13 (26.0)
MGMT promoter methylation	Methylated	16 (43.2)
(IDH-wildtype, n = 37)	Unmethylated	21 (56.8)
ATRX expression	Loss	11 (84.6)
(IDH-mutant, n = 13)	Retained	2 (15.4)
Overall survival (months)	Median (95% CI)	16.5 (13.2–20.1)

†Cochran–Armitage test for trend.

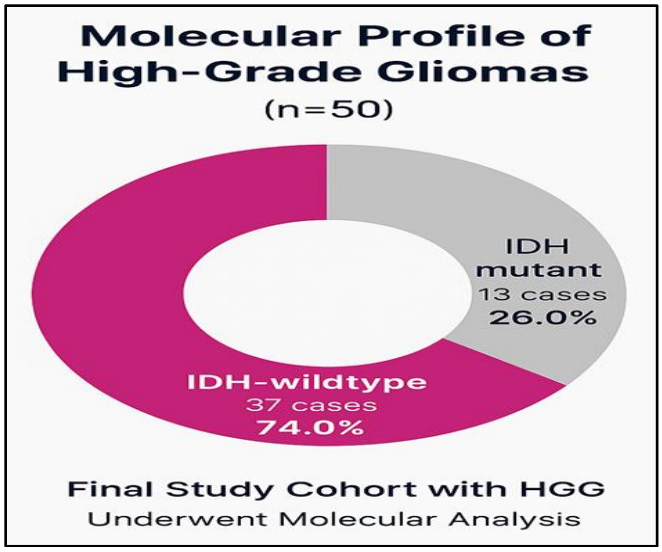

Figure 1: *showing the percentage of molecular profiling of tumors in terms of IDH mutant and wild type.*

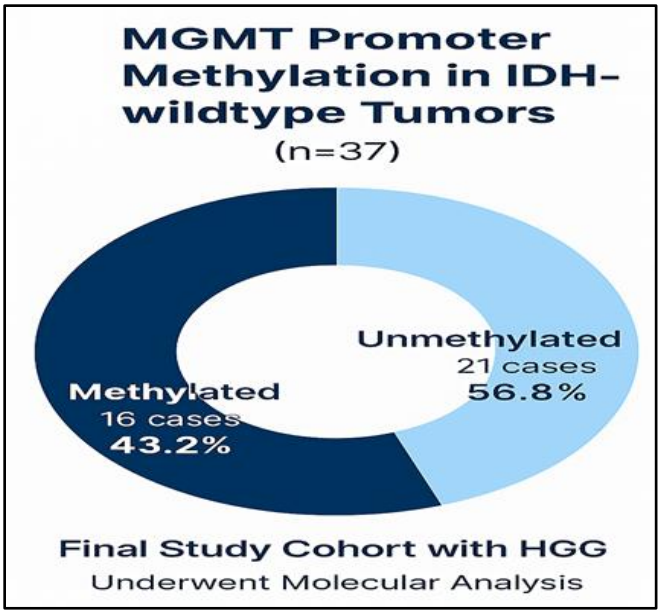

Figure 2: *showing the percentage of IDH methylation in wild-type tumors.*

DISCUSSION

Patient Cohort and Overall Outcomes

We retrospectively analyzed 85 young adults aged 18 to 39 years diagnosed with high-grade gliomas. Two findings were most striking: the tumors had very aggressive biology with a high proportion (74%) being IDH wild-type, and their median overall survival was only 16.5 months. Even though patients were young, their survival statistics were poor, which speaks volumes for how bad the disease is.

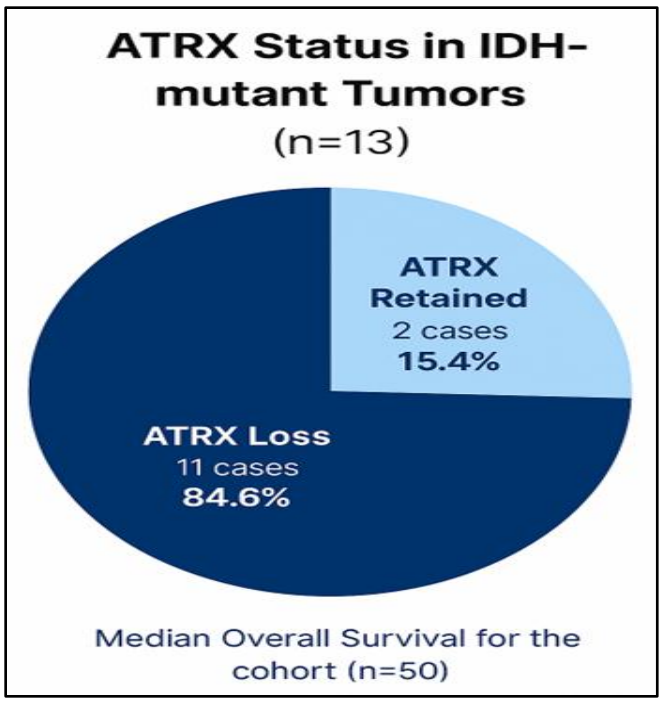

Figure 3: *showing ATRX status in IDH-mutant tumors.*

Prevalence and Impact of IDH-Wildtype Tumors

This high rate of IDH-wildtype tumors is in keeping with past findings pointing to an unfavorable outcome for young adults with HGGs, primarily due to aggressively behaving tumours.[11,12] While it has been established that IDH-mutant gliomas are more prevalent in young individuals, IDH-wildtype glioblastomas are the most common type of this tumor and, regrettably, the deadliest of them all.[13] IDH-wildtype tumor status does not just define a category of tumors; it impacts survival.

MGMT Promoter Methylation and Treatment Implications

Among the IDH-wildtype tumors, 43% carried the MGMT promoter methylation. This is clinically relevant because MGMT methylation diminishes DNA repair capacity in tumors and enhances their sensitivity to alkylating chemotherapy, such as temozolomide.[14,15] Compared with other studies, the rather higher rate of MGMT methylation in our cohort may be representative of regional or age-related differences. Whatever the reason, this again emphasizes the importance of routine MGMT testing in young adults with HGGs. Indeed, close to half of these patients could gain more benefit from the standard chemoradiotherapy treatment based on this molecular characteristic.

IDH-Mutant Tumors and ATRX Loss

About a quarter of tumors in our cohort were IDH-mutant, and the majority of these also demonstrated ATRX loss. Patients with IDH-mutant tumors generally had better outcomes[16,17]. These findings further emphasize that accurate molecular characterization is essential for proper diagnosis, prognostication, and treatment planning in young adults with HGGs.

Because molecular profiling was not available for all patients, these findings should be interpreted as representative of the tested subset rather than the entire cohort.

Survival in the Context of Existing Literature

The median overall survival, at 16.5 months, also correlates well with previously reported overall survival rates for glioblastoma, which vary between 12 and 18 months, even in the context of standard therapy.[17,18] This also indicates that age is unlikely to impact prognosis in any meaningful way, and tumor biology, particularly IDH-wildtype, remains the most important determinant. Younger individuals may tolerate aggressive therapy, but ultimately, biological aggressiveness determines outcome.

Survival outcomes should be interpreted with caution because treatment intensity and compliance could not be uniformly assessed. Variations in radiotherapy dosing, chemotherapy exposure, and treatment adherence may have influenced survival estimates.

Long-Term Survivors and Factors Associated with Better Outcomes

Although on average, survival figures are low, a minority of IDH-wildtype glioblastoma patients seemingly defy these odds and achieve long-term survival.[19] The prognosticators in such cases appear to be MGMT promoter methylation, maximum safe resection, and successful first-line therapy with long-lasting disease control. The overall high incidence of MGMT methylated tumours in this cohort may also, in part, contribute to the good survival in these younger patients, emphasizing the need for maximizing standard treatment protocols.[20]

Need for Individualized Treatment Strategies

The Management of HGGs in young adults should not rely entirely on conventional treatment algorithms. Instead, a personalized approach beginning with comprehensive molecular profiling is essential. Temozolomide-based chemoradiotherapy remains an essential treatment, particularly for patients with MGMT-methylated tumors.[18,21] For IDH-mutant tumours, further research is needed to elucidate the implications of frequent ATRX loss and to identify therapeutic targets.

Psychosocial and Quality-of-Life Considerations

Making a diagnosis of HGG during early adulthood has the following implications for the individual as well as for society. It affects the individual's education, job opportunities, relationships, and plans for bringing up a family. Similarly, the neurological effects, cognitive impairment, and mental health issues create a challenge to the quality of life. It is important, therefore, to address care interventions not only in the cancer aspect but also in psychosocial issues at the early stage of the disease. Therefore, young adults need care models that address special problems during this stage of their lives.

Equity in Access to Molecular Diagnostics and Care

There are existing disparities in terms of the presence or absence of molecular diagnostics and advanced therapies. It is, therefore, very important that these disparities are addressed to ensure that all young adults suffering from HGGs are provided with crucial care, irrespective of their socio-economic and geographical factors. Equity in care delivery is not optional, but it is an obligation.

LIMITATIONS

This study has several limitations. First, its retrospective design introduces potential selection and information bias. Second, molecular profiling was available for only 50 of 85 patients, and molecular subgroup analyses were therefore limited to this subset, which may affect representativeness and generalizability. Third, although the extent of resection was documented, surgical decision-making was influenced by tumor location and biological aggressiveness, particularly in deep-seated or brainstem tumors, which may confound survival interpretation. Fourth, postoperative neurological complication rates were not consistently recorded and could not be reliably quantified. Fifth, detailed treatment parameters, including radiotherapy dose, number of temozolomide cycles, and treatment adherence, were not uniformly available, limiting assessment of therapy-outcome relationships. Finally, survival was not stratified by molecular subgroups such as IDH mutation status due to the limited sample size within the tested patients. Prospective studies with standardized surgical, molecular, and treatment documentation are required to validate these findings.

CONCLUSION

This study demonstrates the complexity and challenges of high-grade gliomas in young adults. Most tumors in this age group are aggressive and are classified as IDH-wildtype glioblastomas. With a median survival of only 16.5 months, the burden of this disease remains severe. A major takeaway is the importance of detailed molecular testing for every patient, particularly MGMT promoter methylation status, as it helps predict who is more likely to respond to standard treatments. Moving forward, research needs to go beyond single treatment approaches. Efforts should focus on identifying new biological targets, designing clinical trials specific to young adults, and making survivorship care a routine part of management. The goal should be not just longer survival, but a better quality of life for young adults living with high-grade glioma.

Conflict of Interest

The authors declare no conflicts of interest related to this manuscript. No financial or personal relationships affected the conduct or reporting of this study.

Ethical Approval

This retrospective study received approval from the Institutional Review Board (No. 2409/IRB/PINS/Approval/2025). As the research used anonymized data and reviewed existing records, the board waived the requirement for individual informed consent.

Disclosure / Use of AI Statement

Use of Artificial Intelligence: The authors declare that a generative AI tool (ChatGPT by OpenAI, GPT-5.2) was used solely for **English language editing and grammatical refinement** of the manuscript. The AI tool was not used for study design, data analysis, data interpretation, or the generation of scientific content. All scientific responsibility for the content rests entirely with the authors.

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AUTHOR CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Adeel Ur Rehman	1. Study design and methodology.
2.	Sikandar Ali	2. Paper writing.
3.	Samra Majeed	3. Data collection and calculations.
4.	Hammad Nasir	4. Analysis of data and interpretation of results.
5.	Toqeer Ahmed	5. Literature review and referencing.
6.	Nida Gulzar	6. Editing and quality insurer.
7.	Ahmad Akhtar Rashid	7. Editing and quality insurer.
8.	Hafiz Abdul Majid	8. Supervision and Validation, quality insurer.