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Prognostic Importance of Histomolecular Subtyping of Central Nervous System Gliomas in Low and Middle-Income Countries

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Background Access to advanced histomolecular diagnostic testing for central nervous system (CNS) tumors is limited in low and middle-income countries (LMICs), hindering adequate characterization and failure to reach a WHO CNS 2021 diagnosis. LMICs also lack access to targeted therapies, and even conventional chemotherapy and radiation therapies vary between LMICs and high-income countries. Consequently, whether histomolecular subclassification is clinically beneficial and if it provides prognostic information in an LMIC setting is not clear. Here, we address this question by presenting the first systematic prospective study of CNS glioma patients from Pakistan, examining differences in overall survival (OS) by histomolecular subtype.

Methods A total of 194 patients with CNS tumors were enrolled at a single tertiary-care center in Karachi, Pakistan. Routine histochemical processing, immunohistochemistry, and molecular testing using fluorescence *in situ* hybridization analysis, limited targeted-panel next-generation sequencing, and polymerase chain reaction were performed to test for isocitrate dehydrogenase (IDH) 1 and 2, P53, ATRX, Ki-67, 1p/19q co-deletion, and MGMT promoter methylation.

Results The results revealed that IDH status was a significant independent prognostic factor, regardless of age (p=0.016), with a 1-year survival rate of 76% and median OS of 16.15 months in IDH-wildtype high-grade gliomas. Conversely, the 1-year survival rate was 95% for IDH-mutant gliomas. Significant survival differences were observed for ATRX status (retained vs. loss) in IDH-mutant gliomas (p=0.046), P53 mutations in IDH-wildtype high-grade gliomas (p=0.05), and 1p/19q co-deletion in grade 3 gliomas (log-rank p=0.023).

Conclusion We provide empirical evidence supporting a role for histo-morphological and limited molecular testing in neuro-oncology practice in LMICs.

Keywords Neuro-oncology; Glioma; Histomolecular; Kaplan–Meier; Low and middle-income countries.

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INTRODUCTION

Central nervous system (CNS) gliomas pose a significant and growing challenge worldwide, including in low and middle-income countries (LMICs) [1]. The rising incidence of CNS gliomas can be attributed to improved diagnostic methods, an aging population, and advancements in treatments for communicable diseases and trauma [2]. The diagnosis and treat-

ment of CNS tumors have undergone significant transformation with the introduction of molecular diagnostics and targeted therapies. In particular, the WHO Classification of CNS Tumors, updated in 2021, employs both traditional histomorphology and molecular alterations for a "layered integrated diagnosis" [3,4]. Molecular subtyping has been shown to improve prognostication and guide management [5]. Newer treatments such as targeted therapies, tumor-treating fields, and local chemotherapy implants have high costs [6], leading to a widening gap in CNS management practices between LMICs and high-income countries.

Recent advances in molecular diagnostics have significantly improved our understanding of glioma biology and classification. Several key molecular markers are now routinely used in clinical practice, providing valuable diagnostic, prognostic, and predictive information [7,8]. The integration of histomolecular diagnosis and subtyping can better predict tumor recurrence and overall survival (OS). For example, isocitrate dehydrogenase (IDH)-mutated tumors show significantly better survival compared to IDH-wildtype glioblastomas [9]. It has been proposed that epigenetic patterns seen with the presence of IDH1 mutations push gliomas towards stem cell-like states, encouraging mutations that lead to tumorigenesis [10]. At the same time, these epigenomic modifications give these tumors a signature pattern that can be recognized on whole genome epigenomic profiling [11,12]. TP53, a well-known tumor suppressor gene, Ki-67, an indicator of the proliferative index, and ATRX gene mutations may confer additional prognostic information in certain gliomas [13,14]. Despite the well-established importance of these markers for diagnosis and prognosis, molecular testing for these markers has limited availability, and few studies have reported on the molecular features of CNS tumors in LMICs, leaving a large gap in our global understanding of the brain tumor burden of this disease.

There are substantial global disparities in the diagnosis, treatment, and outcomes of gliomas, with particularly pronounced challenges in low and middle-income countries [15]. While survival differences by molecular markers such as IDH, p53, MGMT, ATRX, and 1p/19q co-deletion are well established in high-income settings, their prognostic relevance in LMICs remains unclear. This study addresses this gap through a prospective analysis of glioma cases treated at an academic center in Karachi, Pakistan.

MATERIALS AND METHODS

We conducted a prospective cohort study at Aga Khan University Hospital, Karachi, Pakistan, including 194 consecutive cases diagnosed with glioma, according to the WHO 2016 classification of CNS tumors [16]. Six patients underwent repeat surgery for tumor recurrence. All cases were reclassified by a board-certified neuropathologist according to the WHO 2021 criteria. The study included patients treated between September 2019 and October 2024 who underwent elective brain tumor surgery, provided informed consent, and were diagnosed with glial neoplasms. Data on patient characteristics (age, tumor location, Karnofsky Performance Score [KPS] at baseline, postoperatively, and at last follow-up), treatment data (chemotherapy, radiation therapy and extent of surgical resection), histopathology, tumor grade, and molecular markers (IDH, p53, Ki-67, ATRX, 1p/19q co-deletion, MGMT promoter methylation) were retrieved from hospital medical records. Patients were followed up in the clinic after surgery for adjuvant treatment referrals. A routine postoperative MRI was conducted within 72 hours after surgery to evaluate the extent of tumor removal.

Immunohistochemical analysis was performed on archived FFPE tissue blocks to determine the prevalence of four biomarkers: IDH1 R132H, p53, ATRX, and Ki-67 across glioma cases. Tissue sections (4 μm) were prepared using a microtome for analysis. The sections were deparaffinized and rehydrated by placing the samples in xylene for 2 min followed by immersion in 100%, 90%, 80%, and 70% alcohol for 3 minutes each. Tissue sections were stained using mouse monoclonal antibody against IDH1 (IDH1 R132H, clone: H09, Dianova), ATRX (clone: BSB-108), and p53 (DO7, Cell Marque) according to the manufacturers' instructions. Each IHC slide was examined under a light microscope (OLYMPUS BX43) by an independent board certified histopathologist. MGMT and 1p/19q co-deletion status were collected from hospital records where performed. 1p/19q co-deletion was examined via FISH analysis, and MGMT was performed using the Multiplex Ligation Probe Assay (MLPA).

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp.), Stata 15 (StataCorp.), and R (version 4.5.1; R Foundation for Statistical Computing). Data were assessed for normality according to the Kolmogorov–Smirnov test, and descriptions of variables were calculated in terms of the mean±standard deviation or the median±interquartile range (IQR) for non-normal data. Comparisons were made between tumor grades and according to molecular marker subtypes (cases of pilocytic astrocytoma and ependymomas were grouped in category of "other glioma"). Survival was analyzed using the Kaplan–Meier method with comparisons between molecular subgroups made using the log-rank test. Overall survival was assessed at 12, 24, and 60 months, with $p \leq 0.05$ considered statistically significant.

The study was approved by the institutional ethical board (ERC No. 2019-1945-5110, ERC No. 2021-1945-17282, ERC No. 2021-6265-18766). Written informed consent has been

obtained from all participants to publish this paper.

RESULTS

A total of 10 (6%) pediatrics and 184 (94%) adult patients were included in this study. The mean age of patients was 36 (±15.5) years. Female patients constituted 35% of the sample, reflecting the well documented underrepresentation of females presenting for surgical care for CNS tumors in Pakistan [17]. The median preoperative KPS was 70 (IQR 70–80) for the cohort; the median postoperative KPS was 80 (IQR 70–90). Gross total or near-total resection was achieved in 52.1% (n=101) of the cohort, with seven biopsy procedures (3.6%), and 44.3% (n=86) had subtotal resections. KPS improved postoperatively within a duration of 3–6 months (median KPS: preoperative=70, IQR 70–80; postoperative=80, IQR 70–90, $p<0.001$).

Table 1. Demographic and clinical characteristics of the cohort (n=194)

Clinical features	Count (%)
WHO 2021 diagnosis	
Glioblastoma, IDH-wildtype, grade 4	63 (32.5)
Astrocytoma, IDH-mutant	55 (28.4)
Oligodendroglioma, IDH mutant & 1p/19q codeleted	41 (21.1)
Unclassified	19 (9.8)
Others	16 (8.2)
WHO 2021 grade	
Grade 1	15 (7.7)
Grade 2	55 (28.4)
Grade 3	41 (21.1)
Grade 4	83 (42.8)
Age group	
0–19 yrs	18 (9.3)
20–39 yrs	86 (44.3)
40–65 yrs	80 (41.2)
>65 yrs	10 (5.2)
Age	
Mean age	38 years
Sex	
Female	67 (34.5)
Male	127 (65.5)
Tumor	
Primary	161 (83.0)
Progression	8 (4.1)
Recurrent	25 (12.9)
Surgery	
1st	163 (84.0)
2nd	28 (14.4)
3rd	3 (1.5)
Extent of resection	
Biopsy	7 (3.6)
Gross total resection	91 (46.9)
Near-total resection	10 (5.2)
Subtotal resection	86 (44.3)
Chemotherapy	
No	65 (33.5)
Yes	129 (66.5)
Radiotherapy	
No	58 (29.9)
Yes	136 (70.1)

IDH, isocitrate dehydrogenase.

The histomolecular profile of the cohort is summarized in Table 1. The most common tumors in the cohort included glioblastoma (63 cases), IDH-mutant astrocytoma (55 cases), and IDH-mutant oligodendrogliomas (41 cases), while unclassified gliomas (19 cases) and other gliomas (16 cases) (14 pilocytic astrocytoma, 2 ependymoma cases) were less common.

Survival data were available for 193 patients (1 patient lost to follow-up), and molecular markers were available for IDH (179 cases applying IHC and MLPA Multiplex Prob-based PCR Analysis), p53 (182 cases), ATRX retention/loss (169 cases), Ki-67 status (184 cases) applying IHC, 1p/19q co-deletion (65 cases through FISH fluorescence *in situ* hybridization), and MGMT promoter methylation status (34 cases through MLPA Multiplex Prob-based PCR Analysis). Fig. 1 shows the Kaplan–Meier curves for OS and the survival rates within individual molecular subgroups of the cohort; IDH-wildtype glioblastoma shows 18 months of median OS.

Median OS was evaluated in patients with at least 12 months of postoperative follow-up. Survival outcomes according to histopathological subgroups and molecular markers (IDH: n=179, p53: n=182, ATRX: n=169, 1p/19q co-deletion: n=65, and MGMT promoter methylation: n=34) are summarized in

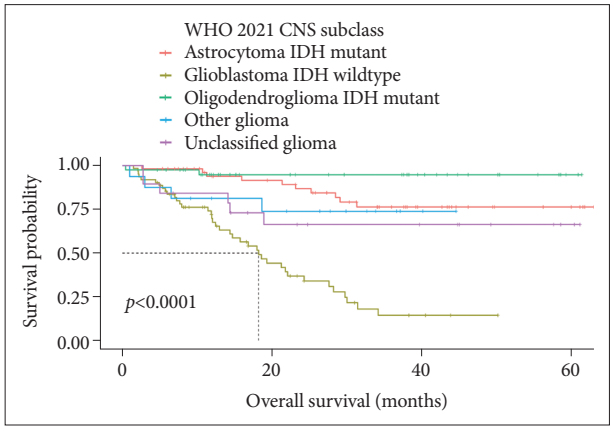

Fig. 1. Kaplan–Meier curves analyzing major tumor types in our cohort (IDH-wildtype glioblastoma, compared to other histological tumor types, is associated with median overall survival of approximately 18 months). CNS, central nervous system.

Table 2. Overall survival according to histopathological subgroups and molecular markers (12-month follow-up)

WHO 2021 diagnosis	OS (mo); median (IQR)
Histopathological subgroups	
Astrocytoma 2	40.6 (31–59.96)
Astrocytoma 3	36.17 (26.19–43.42)
Astrocytoma 4	19.37 (11.3–37.8)
Oligodendroglioma 2	37.57 (13.6–48.18)
Oligodendroglioma 3	37.33 (13.07–42)
Other glioma	27.07 (11.2–34.53)
Unclassified glioma	23.33 (14.23–47.13)
Glioblastoma 4	12.23 (6.8–21.99)
Molecular markers	
IDH wildtype	16.73 (7.45–29.86)
IDH mutant	29.63 (11.78–42.7)
P53 wildtype	16.8 (8.13–37.33)
P53 mutant	25.32 (11.39–40.43)
ATRX retained	18.57 (8.4–38.26)
ATRX loss	29.07 (15.15–39.31)
1p/19q co-deleted	37.33 (10.95–45.5)
1p/19q not deleted	29.87 (16.13–45.9)
MGMT methylated	23.33 (11.58–46.66)
MGMT unmethylated	12.43 (11.88–16.21)

OS, overall survival; IQR, interquartile range.

Table 2. Molecular profiles were not conducted on every consecutive sample resulting in differing denominators. Pilocytic astrocytoma were merged in other gliomas.

Fig. 2A shows significant differences in survival for IDH-wildtype glioma across age groups (p=0.016), with patients 40 years or above showing median OS of 18 months. However, no significant difference in survival was seen between IDH-wildtype gliomas when stratified by ATRX status (p=0.756) (Fig. 2B). Fig. 2C shows that P53 mutation has better OS in high-grade glioma (grade 4, median OS of 25.8 months) (p=0.007). Fig. 2D depicts the good prognosis in IDH-wildtype tumors with MGMT promoter methylation (p=0.054), while MGMT promoter without methylation shows 12.3 months for median OS.

Fig. 3A shows that IDH-wildtype gliomas have significantly worse (14.4 months median) OS (log-rank p<0.0001) compared to IDH-mutant gliomas. Fig. 3B shows that a loss of ATRX is associated with a worse prognosis for IDH-mutant gliomas but not within IDH-wildtype gliomas, mirroring worse OS in IDH-mutant astrocytoma compared to oligodendroglioma. Similarly, 1p/19q co-deletion status is associated with better survival, as shown in Fig. 3C and D; however, in our data, this benefit was restricted to grade 3 gliomas (p=0.023), with no significant difference in grade 2 tumors.

MGMT methylation status was not associated with a better outcome in IDH-mutant glioma (Supplementary Fig. 1 in the online-only Data Supplement) but showed a trend towards better survival in IDH-wildtype gliomas. The life tables (Supplementary Tables 1 and 2 in the online-only Data Supplement) show differences, with 1-year survival at 95% for IDH-mutant and 76% for IDH-wildtype gliomas. At the 3-year survival point, 86% of IDH-mutant cases were still alive, with only 37% survival in the IDH-wildtype cohort. Significant survival differences are seen for ATRX in IDH-mutant tumors (log-rank p=0.046); as shown in Fig. 3B, the 1-year survival rate varies from 86% (ATRX-loss) to 98% (ATRX-retained), while the 3-year survival rate varies from 74% (ATRX-loss) to 91% (ATRX-retained). 1p/19q co-deletion status for grade 3 gliomas (log-rank p=0.023) are given in Fig. 3D. P53-mutant gliomas showed better survival trends within the IDH-wildtype cohort (p=0.05) (Supplementary Fig. 2 in the online-only Data Supplement).

Fig. 4 presents the results of the Cox regression analysis for survival predictors. In the univariate analysis (Supplementary Fig. 3 in the online-only Data Supplement), age over 45 years, IDH-wildtype, high Ki-67 index, and postoperative KPS below 70 were all associated with poor OS. However, in the multivariate analysis, only postoperative KPS and IDH status remained significant predictors.

Histomolecular classification showed a significant association with survival outcomes in our cohort, with glioblastoma multiforme (GBM) and other high-grade gliomas demonstrating worse prognosis compared to astrocytoma, IDH-mutant gliomas, low grade gliomas, and oligodendrogliomas.

DISCUSSION

Gliomas are the most common primary brain tumor, with a significant impact on mortality and quality of life. In Europe, approximately 27,000 new cases of malignant glial tumors are diagnosed annually [18]. In the United States, an estimated 17,000–18,820 new cases are reported each year, with GBM accounting for approximately 7,000–8,000 cases [19,20]. Gliomas in LMIC patients remain poorly characterized and understudied. We present the first systematic prospective study of histo-molecularly characterized gliomas in Pakistan, the fifth largest country in the world with a population of over 230 million. The Pakistan Brain Tumor Epidemiology Study analyzed data from 32–35 neurosurgical centers across Pakistan, revealing approximately 781–2,750 glioma cases in 2019 [21]. Prior to this study, only one retrospective study from Pakistan had studied the correlation of IDH, EGFR, MDM2, and P53 molecular markers with OS in gliomas [22]. This study presents the first prospective analysis of CNS gliomas in Pakistan, highlighting the prognostic value of molecular subtyping within this population. By correlating survival outcomes

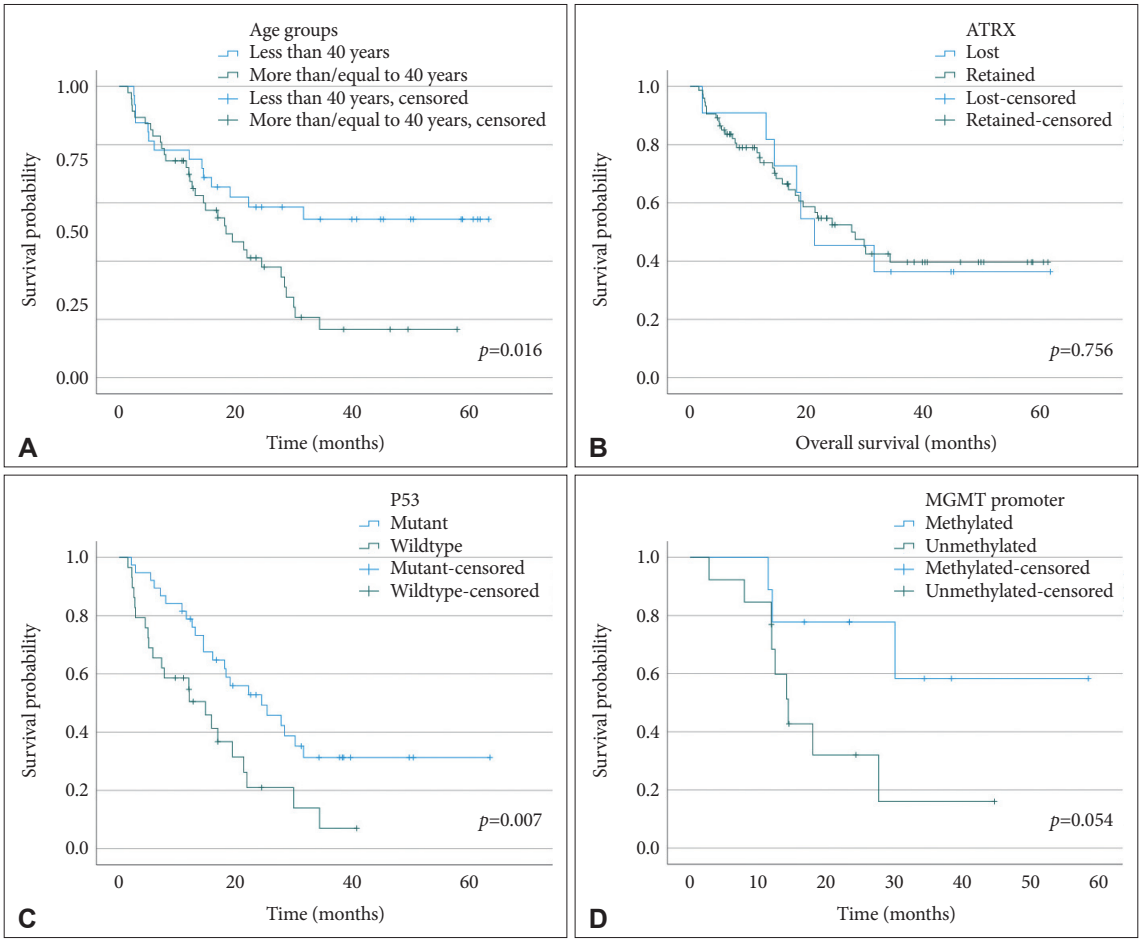

Fig. 2. Kaplan–Meier curves for overall survival in IDH-wildtype gliomas according to molecular subgroups. A: Overall survival stratified by age group. B: Overall survival according to ATRX status. C: Overall survival according to P53 mutation status in grade 4 gliomas. D: Overall survival according to MGMT promoter methylation status.

with key molecular markers such as IDH mutation, Ki-67 index, and MGMT promoter methylation, this study demonstrates that updated molecular classifications enhance prognostic precision and guide treatment decisions. Reclassification under the WHO 2021 criteria revealed major shifts in grading and management, highlighting the need to strengthen molecular testing in LMICs (Supplementary Fig. 4 in the online-only Data Supplement). Consistent with international data, our findings show poorer survival for grade 4 IDH-wildtype glioblastomas (median OS: 14.2 months), underscoring the global relevance of molecular epidemiology in understanding survival trends. Our work expands on previous reports from Pakistan where significant survival differences could not be seen when stratifying by IDH mutation status, which may have been affected by patients lost to follow-up and other factors affecting glioma survival [23]. We benefitted from a prospectively designed study with the intention of conducting consistent follow-ups and using a cohort with better radiotherapy and chemotherapy completion rates than previously been reported in this region [21]. MGMT promoter methylation is an epigenetic change that ties in with IDH-wildtype glioma survival and with predicting benefit from temozolomide and prolonged survival in this subset of gliomas. This has been a useful biomarker, particularly within elderly glioblastoma patients, and has been shown to have a significant prognostic value when deciding on the survival benefit of chemotherapy or radiotherapy in phase III clinical trials [24]. Although limited by sample size and the high cost of testing, our findings indicate a significant survival benefit in patients with MGMT promoter-methylated gliomas.

Investigations into the p53 pathways in glioblastoma suggest that MDM2 acts as an oncogenic inhibitor of p53-mediated tumor suppression, inactivating p53 and leading to a loss of cell cycle arrest and DNA repair mechanisms. MDM2 amplification occurs only in p53 wildtype GBM, which may explain the significant difference in grade 4 p53-mutant and -wildtype glioma OS seen in our cohort [25]. Molecular interactions between TP53 and MDM2, as shown in Supplementary Fig. 5 (in the online-only Data Supplement), highlight their role in glioma progression and survival. The 1p/19q co-deletion was

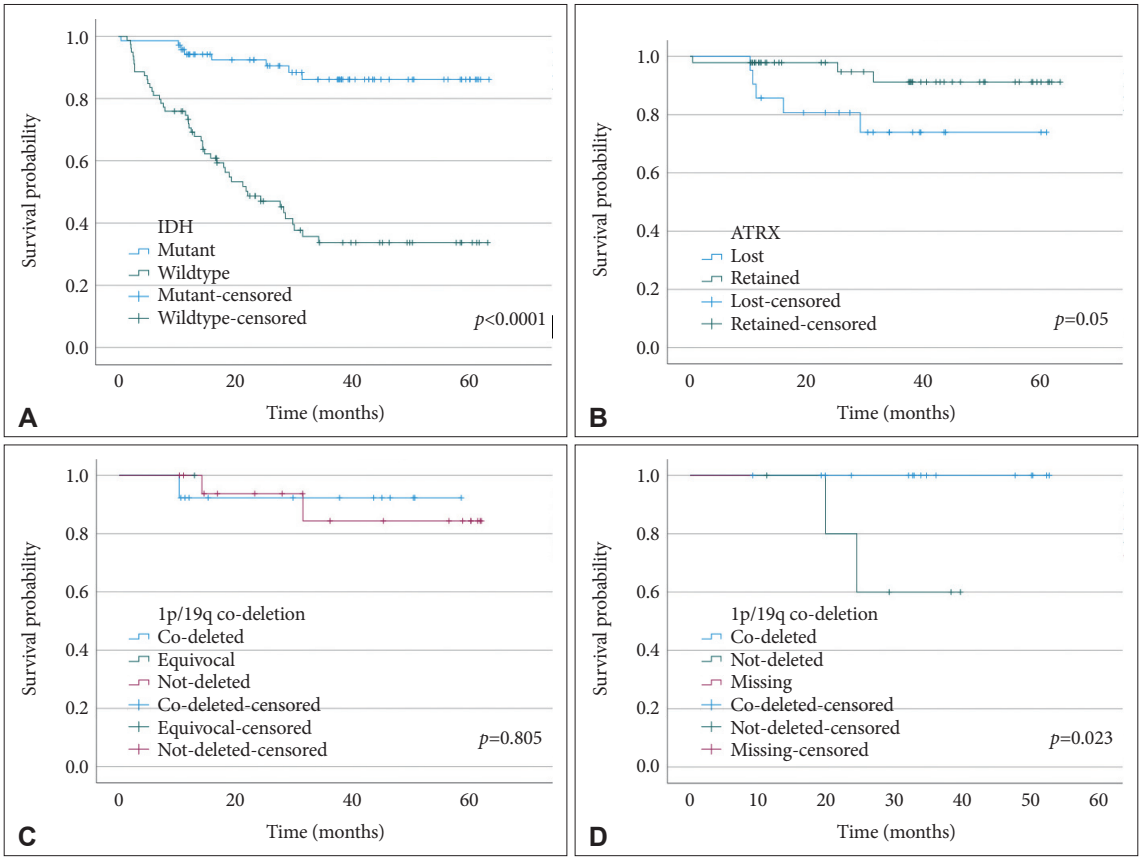

Fig. 3. Kaplan–Meier curves for overall survival according to molecular subgroups. A: Overall survival in IDH-wildtype vs. IDH-mutant gliomas (p<0.0001). B: Overall survival according to ATRX status in IDH-mutant gliomas. C and D: Overall survival according to 1p/19q co-deletion status in grade 2 (C) and grade 3 (D) gliomas, respectively (grade 3: p=0.023; grade 2: not significant). All p-values were calculated using the log-rank test.

confirmed as a protective factor, while IDH mutation status remained the most significant prognostic marker, particularly in younger patients. In older adults, histopathological grade showed stronger prognostic value, emphasizing the continued relevance of traditional grading. Notably, IDH-wildtype 2 gliomas exhibited better survival than expected, suggesting molecular heterogeneity within this group. Overall, both molecular and histopathological factors complement each other in predicting outcomes, reinforcing the importance of integrated classification in glioma management. However, there are significant advantages to our data, as this is one of the few long-term patient follow-up studies documenting survival outcomes within the context of treatment and molecular signatures [26]. We have also shown reclassification of previously diagnosed gliomas according to the 2016 classification with comparison to the new WHO 2021 classification, which has not previously been reported in the literature. While recognizing our limitations, we see a need to further utilize molecular signatures for glioma survival prediction in resource-limited areas and develop robust registries from our populations. In most LMICs, advanced molecular testing is often not available or standard practice due to constraints; our evidence shows a need for greater implementation of molecular subclassification to appropriately prognosticate tumors. Furthermore, our data show comparable results with what has been reported from other international centers recently (Supplementary Table 3 in the online-only Data Supplement). Grade 4 IDH-wildtype survival outcomes are comparable to what is reported from international centers.

We have previously demonstrated that advanced molecular testing can provide valuable information for management decisions in high-grade tumors, essentially by differentiating gliomas from other high-grade, morphologically similar tumors, such as embryonal tumors and ependymomas. In this study, high-grade gliomas aligned with GBM, showing potentially low yield for these tests. Histological grade was associated with survival differences, suggesting that even in the era of molecular diagnostics, classic histopathological examination remains a valuable source of information.

We have observed lower OS among CNS glioma patients in Pakistan compared to in high-income countries. Several factors may contribute to this difference. Previous reports have

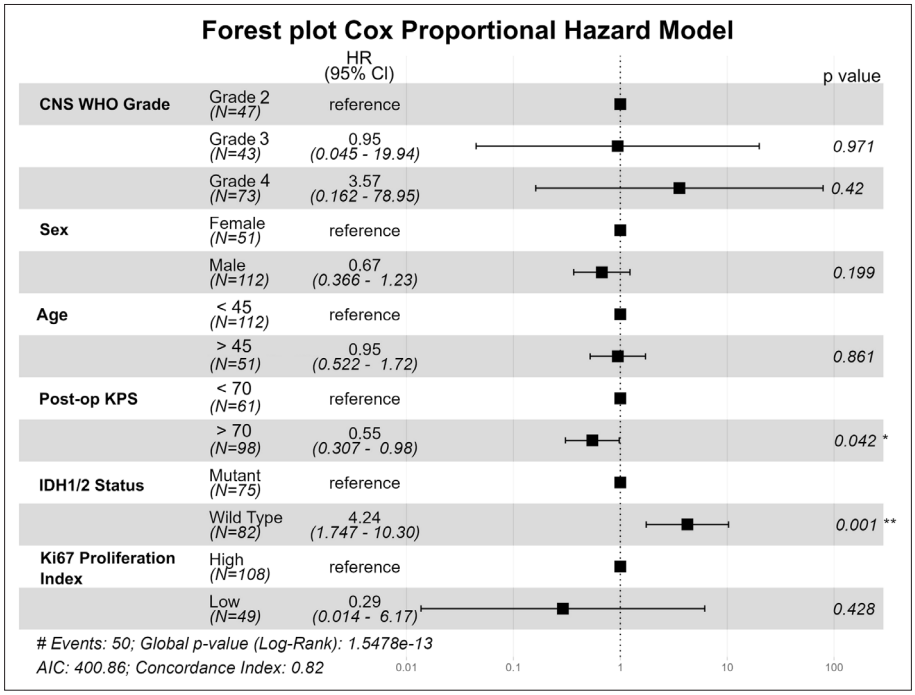

Fig. 4. Forest plot from Cox proportional hazards model. Hazard ratios (HRs) with 95% confidence intervals (CIs) are shown, adjusted for grade, sex, age group, postoperative KPS, IDH1/2 status, and Ki-67 proliferation index. HR >1 indicates increased risk of event, while HR <1 indicates reduced risk. Proportional hazards assumption was assessed using Cox proportional method with log-rank test. *p<0.05; **p<0.01.

shown treatment patterns of glioma and brain tumor care within this country; beyond budget constraints, there are overarching issues with patients being lost to follow-up, facing barriers to access due to distance traveled, and experiencing disparities in care with regard to gender and public versus private sector hospitals [17,21,27-29].

A limitation of this study is that most tumor subclassification relied on surrogate immunohistochemical markers, with nucleic acid–based or methylation profiling performed in only a few cases. A tiered testing approach was applied, reserving advanced methods for unresolved cases. Nonetheless, this aligns with current WHO recommendations, which allow flexibility in using protein, nucleotide, or methylation-based assays depending on tumor type and available resources [30]. Immunohistochemistry significantly improves diagnostic accuracy, especially in challenging cases. The judicious use of a panel of selected immuno-stains is crucial for accurate diagnosis and prognosis prediction in neuro-oncologic pathology [31,32]. Immunohistochemistry provides a rapid, cost-effective approach for molecular subtyping and reliable WHO 2021 classification, even in resource-limited settings. The study's long follow-up period further strengthens its findings.

Although the present study was constrained by the limited availability of complete molecular profiles for all cases due to testing costs, this was largely mitigated by assessing key molecular markers including IDH, p53, Ki-67, and ATRX—in nearly 90% of the cases. Moreover, while the study represents samples from a single center, it provides valuable preliminary insights that can inform and guide larger, multi-center investigations in the future.

In conclusion, our findings demonstrate that histomolecular classification of CNS gliomas is a powerful predictor of OS and serves as an essential prognostic tool. Even with limited molecular testing, the integration of immunohistochemical markers enables accurate classification of most cases according to the CNS WHO 2021 criteria, offering meaningful prognostic insights. These results highlight the clinical value of incorporating molecular profiling into routine diagnostic workflows. While further case-control studies are needed to establish its direct impact on patient management, this work provides a strong foundation for advancing precision diagnostics and improving outcomes in CNS tumor care.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14791/btrt.2025.0046.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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