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Clinicopathological Correlation Of Glioma Patients With Respect To Immunohistochemistry Markers

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ABSTRACT

Background: Following the introduction of molecular subtyping in the 2016 WHO classification for gliomas, it has become essential to evaluate the expression patterns of immunohistochemical (IHC) markers in glioma patients and analyze their clinical relevance across different subgroups.

Objective: This study aimed to evaluate the IHC marker expression profiles in glioma patients and explore their clinical correlations within various subtypes.

Materials and Methods: This retrospective study included 100 patients diagnosed with glioma. IHC staining was performed for markers including isocitrate dehydrogenase 1 (IDH1), ATRX, P53, and Ki-67. Treatment was administered based on the tumor grade. Patients were followed up every three months over a 12-month period. Data analysis was performed using SPSS software version 20.0, and Microsoft Excel was used to create tables.

Results: The majority of patients (52%) were aged 40–60 years, with a slight male predominance (55%). Headache (85%) and seizures (66%) were the most common symptoms, followed by weakness (25%), other symptoms (15%), and altered sensorium (8%). Among 100 tumors graded by WHO, Grade 1 showed no IDH positivity or ATRX loss; Grade 2 had high IDH (76.92%) and moderate ATRX loss (46.15%); Grade 3 showed increased p53 (86.96%) and Ki-67 >5% in 82.61%; Grade 4 had 100% Ki-67 >5% with lower IDH (35%) and ATRX loss (27.5%). Overall, 54% were IDH positive, 34% had ATRX loss, 60% p53 positive, and 69% had Ki-67 >5%. Among histological subtypes, Low-grade tumors like PA and GG showed no IDH positivity or ATRX loss, while DA and AA had moderate to high expression of IDH, ATRX loss, and P53, with increased Ki-67 in AA. P GBM had low IDH and ATRX but high Ki-67 (100%), whereas S GBM showed high IDH, ATRX loss, P53, and Ki-67. ODG had high IDH positivity, moderate P53, and no ATRX loss or Ki-67 elevation, indicating a distinct profile.

Conclusion: IHC profiling of gliomas reveals distinct marker patterns across subtypes, aiding in diagnosis and prognostication. IDH positivity and ATRX loss were common in lower grades, while higher grades showed elevated p53 and Ki-67. These markers are valuable tools in aligning histopathology with molecular classification.

INTRODUCTION:

Tumors of the central nervous system (CNS) account for approximately 1%–2% of all neoplasms.[1] Due to their diverse histological appearances and varying patterns of differentiation, CNS tumors present significant diagnostic challenges.[2] In recent years, advancements in immunohistochemistry (IHC), molecular diagnostics, and biomarker identification have become crucial tools in the diagnosis of brain tumors.[3,4]

The 2016 revision of the WHO classification of CNS tumors marked a significant shift by incorporating molecular markers into tumor classification, moving beyond traditional histopathological evaluation alone.[4,5,6] These molecular markers serve not only as diagnostic tools but also carry prognostic value and guide decisions related to screening, treatment planning, and disease monitoring.[7]

Clinical outcomes in patients with brain tumors are influenced by several factors, including patient age, general health status, extent of tumor removal, histological classification, tumor grade, and specific molecular alterations.[8,9] Gliomas, which exhibit predominantly astrocytic or oligodendroglial features, are the most frequent type of CNS tumors in both children and adults.[10]

Recent research suggests that molecular classification of gliomas offers superior prognostic stratification compared to conventional histological methods.[11] Among the key molecular markers used in glioma diagnosis is the isocitrate dehydrogenase 1 (IDH1) R132H mutation. Clinical management strategies for glioma patients are increasingly being tailored based on the status of these molecular markers.

MATERIALS AND METHODS

The study was conducted at Department of Pathology, Dhanalakshmi Srinivasan Medical College & Hospital, Perambalur, Tamil Nadu

STUDY PERIOD: 2 year

STUDY DESIGN: Retrospective study

SAMPLE SIZE: One hundred patients were included

INCLUSION CRITERIA:

- Patients with radiological, clinical, and histological findings suggestive of gliomas and who underwent surgery at our institution.

EXCLUSION CRITERIA:

- Patients not willing for surgery

ALLOCATION & IMPLEMENTATION:

The donors were chosen according to the established inclusion and exclusion criteria. After surgical excision of the tumor, the part of tumor which was most viable and was devoid of macroscopic evident necrosis was taken as specimen. It was fixed in 10% formalin and sent for histopathology followed by immunohistochemical analysis

The WHO classification system for gliomas was employed to determine the pathological grade of the tumors. Postoperative radiotherapy and/or chemotherapy was administered consistently in accordance with standard recommendations. All patients received treatment comprising maximal surgical resection followed by radiation and chemotherapy based on WHO guidelines. Patients with Grade 1 tumors did not require any additional therapy post-surgery.

Histopathological Evaluation

Slides stained with hematoxylin and eosin were reviewed, and diagnoses were confirmed according to the WHO classification of CNS tumors.

Immunohistochemistry (IHC) Staining

IHC was performed on a representative tissue block from each case. Primary antibodies targeting IDH1, ATRX, p53, and Ki-67 were used for staining. Biocare reagents facilitated the staining process. Two independent observers manually evaluated the slides under a microscope, and all staining procedures followed standard protocols.

IDH-R132H Mutation Detection

The IDH-R132H mutation in glioma patients was identified using immunohistochemistry (IHC) with mutation-specific anti-IDH1 antibodies (HPA035248-100 UL). IDH1 protein expression was assessed, and cases where more than 10% of tumor cells showed positive staining were classified as IDH-R132H mutant [Figures 1 and 5].

ATRX Expression Assessment

ATRX status was evaluated via IHC using a polyclonal antibody (HPA001906-100 UL). Tumors showing over 50% positively stained cells were considered to have retained ATRX expression, while those with less than 50% stained cells were classified as having ATRX loss. Endothelial cells, cortical neurons, and infiltrating inflammatory cells, which consistently stained positive, served as internal controls [Figures 1 and 5].

Ki-67 Analysis

The Ki-67 labeling index was determined by calculating the percentage of malignant cells with positive nuclear staining, assessed visually and quantitatively under a light microscope at 400x magnification. The Ki-67 score represents the proportion of stained tumor cells out of the total malignant cells examined. Cases with more than 5% positively stained cells were considered Ki-67 positive, while those with less than 5% were considered negative.

p53 Expression

p53 immunoreactivity was also evaluated, with tumors showing positive staining in more than 10% of cells classified as having strong p53 expression.

Statistical analysis:

The researchers examined the collected data using Microsoft Excel and Chi Square Test testing techniques. The mean and standard deviation data were computed to assess blood pressure and other vital indicators. Statistical analyses determined which interventions between the study group and control group resulted in significant alterations in vasovagal responses. An study of p-values established statistical significance by confirming that the results were not attributable to random chance.

RESULTS

AGE DISTRIBUTION

The age distribution of patients revealed that the majority were between 40–60 years, accounting for 52% (52 patients). This was followed by 28% (28 patients) in the 20–40 years age group, 14% (14 patients) were above 60 years, and the least affected were in the 0–20 years age group, comprising 6% (6 patients).

TABLE 1: AGE DISTRIBUTION

AGE DISTRIBUTION	NO.OF PATIENTS	PERCENTAGE
0-20 YEARS	6	6%
20-40 YEARS	28	28%
40-60 YEARS	52	52%
More than 60	14	14%

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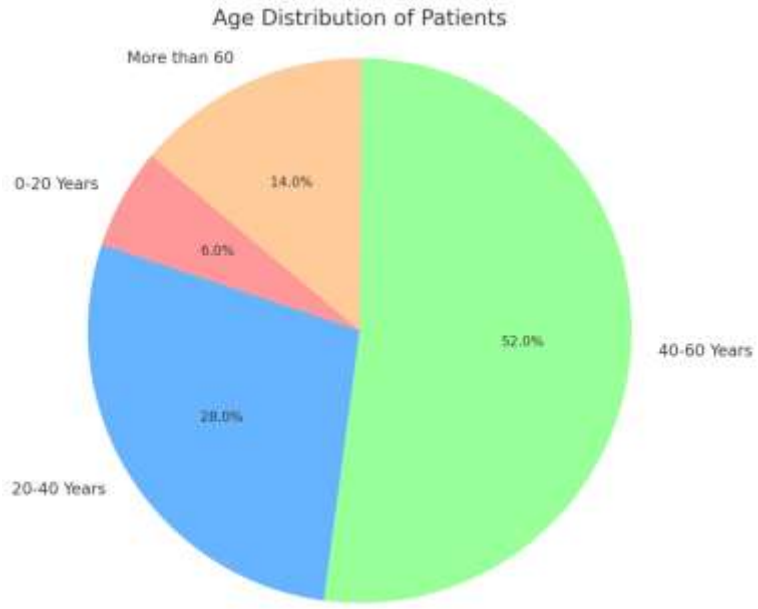
FIGURE 1: AGE DISTRIBUTION



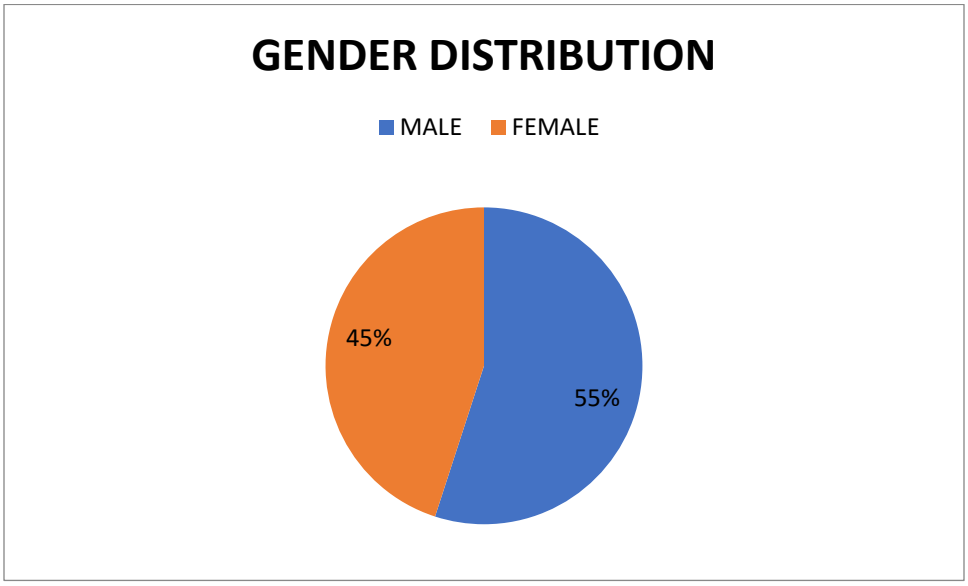
GENDER DISTRIBUTION

Out of the total patients, 55% (55 patients) were male and 45% (45 patients) were female, indicating a slight male predominance.

TABLE 2: GENDER DISTRIBUTION

GENDER	NO.OF PATIENTS	PERCENTAGE
MALE	55	55%
FEMALE	45	45%

FIGURE 2: GENDER DISTRIBUTION



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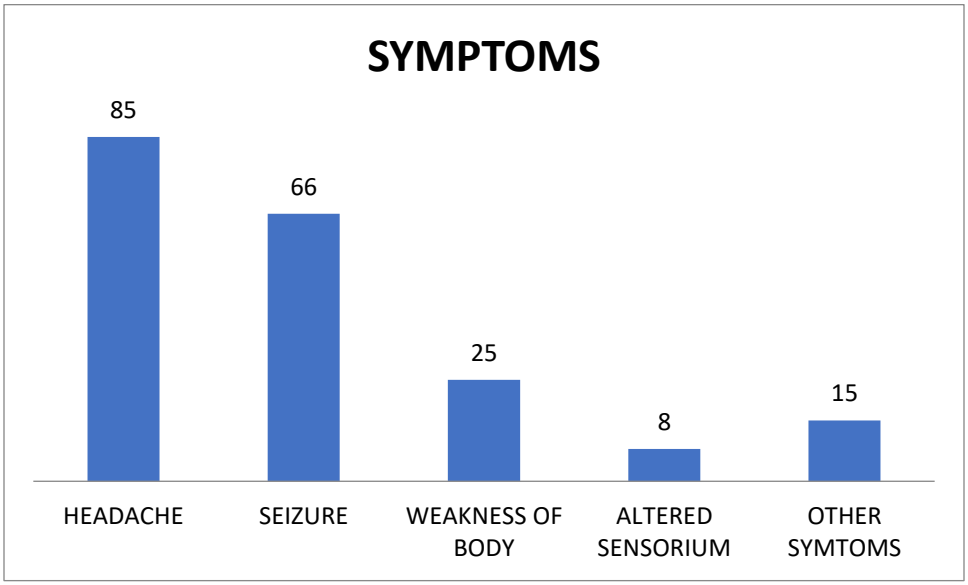
SYMPTOMS

Among the patients, headache was the most common symptom, reported in 85% (85 patients), followed by seizures in 66% (66 patients). Weakness of the body was noted in 25% (25 patients), altered sensorium in 8% (8 patients), and other symptoms were present in 15% (15 patients).

TABLE 3: SYMPTOMS

SYMPTOMS	NO.OF PATIENTS	PERCENTAGE
HEADACHE	85	85%
SEIZURE	66	66%
WEAKNESS OF BODY	25	25%
ALTERED SENSORIUM	8	8%
OTHER SYMTOMS	15	15%

FIGURE 3: SYMPTOMS



IMMUNOHISTOCHEMISTRY ANALYSIS AS PER THE WHO GRADE

Based on WHO grading, 100 tumor cases were analyzed. Grade 1 included 11 cases, with no IDH positivity or ATRX loss, 18.18% showing p53 positivity, and none with Ki-67 >5%. Grade 2 comprised 26 cases, of which 76.92% were IDH positive, 46.15% had ATRX loss, 61.54% were p53 positive, and 7.69% showed Ki-67 >5%. Grade 3 had 23 cases, with 56.52% IDH positivity, 34.78% ATRX loss, 86.96% p53 positivity, and 82.61% showing Ki-67 >5%. Grade 4 included 40 cases, with 35% IDH positivity, 27.5% ATRX loss, 45% p53 positivity, and all cases (100%) showing Ki-67 >5%. Overall, 54% of the cases were IDH positive, 34% had ATRX loss, 60% were p53 positive, and 69% showed a Ki-67 proliferation index greater than 5%.

TABLE 4: Immunohistochemistry analysis as per the WHO grade

WHO	Cases	IDH positive (%)	ATRX loss (%)	P53 positive (%)	Ki-67 >5(%)
Grade 1	11	0 (0.00%)	0 (0.00%)	2 (18.18%)	0 (0.00%)
Grade 2	26	20 (76.92%)	12 (46.15%)	16 (61.54%)	2 (7.69%)
Grade 3	23	13 (56.52%)	8 (34.78%)	20 (86.96%)	19 (82.61%)
Grade 4	40	14 (35.00%)	11 (27.50%)	18 (45.00%)	40 (100.00%)
Total	100	54 (54.00%)	34 (34.00%)	60 (60.00%)	69 (69.00%)

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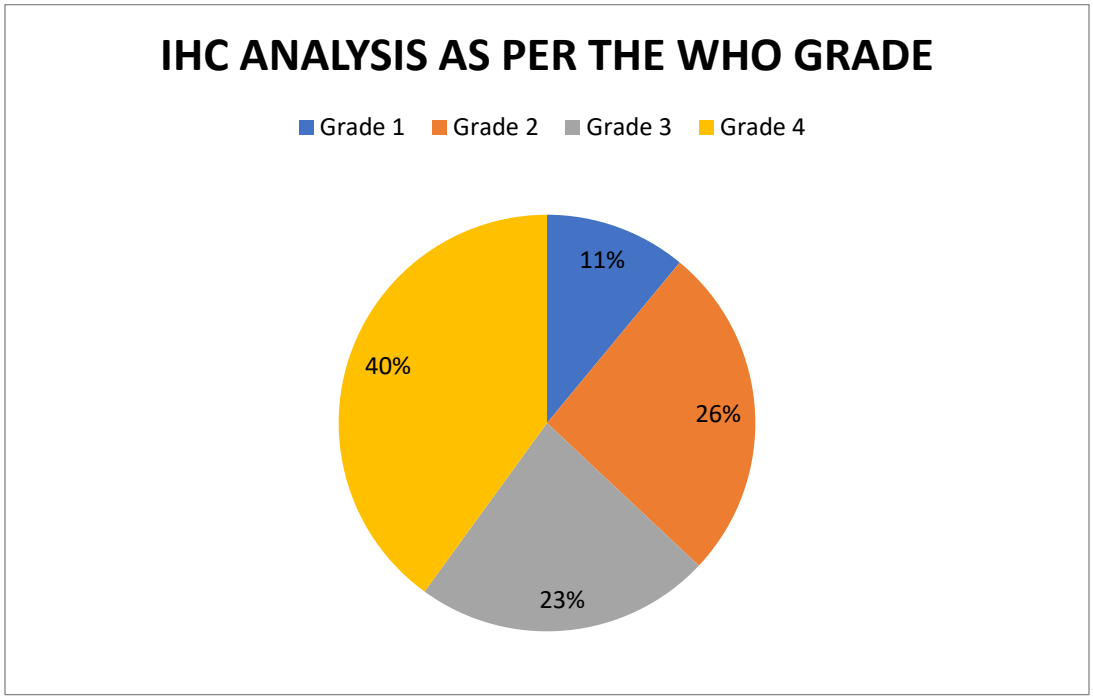

FIGURE 4: Immunohistochemistry analysis as per the WHO grade

IMMUNOHISTOCHEMISTRY ANALYSIS AS PER HISTOLOGICAL DIAGNOSIS

Based on histological subtypes, IDH positivity, ATRX loss, P53 positivity, and Ki-67 index >5%—across various brain tumor types. Pilocytic astrocytoma (PA) and ganglioglioma (GG) showed no IDH positivity or ATRX loss, with only PA exhibiting P53 positivity (40%). Diffuse astrocytoma (DA) showed moderate IDH positivity (65%) and ATRX loss (70%), while anaplastic astrocytoma (AA) had higher rates of all markers, especially Ki-67 >5% in 71.43% of cases. Primary glioblastoma (P GBM) showed low IDH (16.67%) and ATRX (11.11%) expression, but universally high Ki-67 index (100%). In contrast, secondary glioblastoma (S GBM) had high IDH positivity (72.73%) and ATRX loss (63.64%) with similarly elevated P53 and Ki-67. Oligodendroglioma (ODG) demonstrated high IDH positivity (90%) and moderate P53 expression (70%) but lacked ATRX loss and elevated Ki-67, reflecting its distinct molecular profile.

TABLE 5: Immunohistochemistry analysis as per histological diagnosis

Type	Total	IDH positive (%)	ATRX loss (%)	P53 positive (%)	Ki-67 (>5) (%)
PA	5	0 (0.00%)	0 (0.00%)	2 (40.00%)	0 (0.00%)
GG	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
DA	20	13 (65.00%)	14 (70.00%)	10 (50.00%)	2 (10.00%)
AA	14	8 (57.14%)	8 (57.14%)	9 (64.29%)	10 (71.43%)
P GBM	36	6 (16.67%)	4 (11.11%)	11 (30.56%)	36 (100.00%)
S GBM	11	8 (72.73%)	7 (63.64%)	8 (72.73%)	11 (100.00%)
ODG	10	9 (90.00%)	0 (0.00%)	7 (70.00%)	0 (0.00%)

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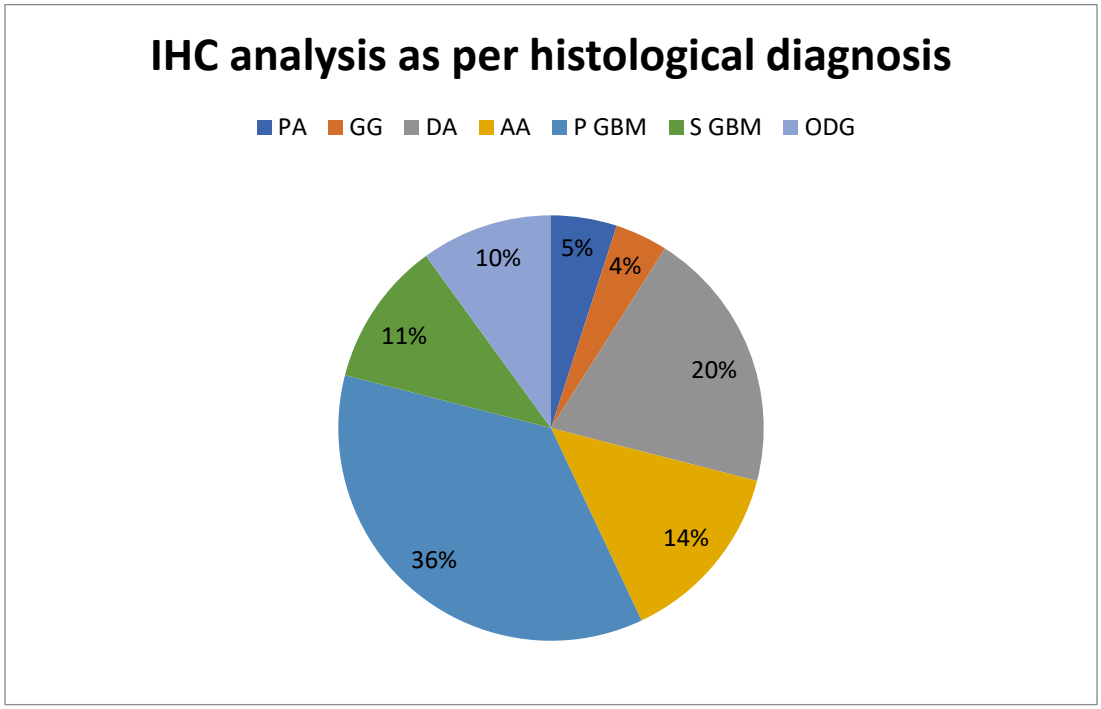

Figure 5: Immunohistochemistry analysis as per histological diagnosis

DISCUSSION

The age distribution of patients revealed that the majority were between 40–60 years, accounting for 52% (52 patients). This was followed by 28% (28 patients) in the 20–40 years age group, 14% (14 patients) were above 60 years, and the least affected were in the 0–20 years age group, comprising 6% (6 patients). Out of the total patients, 55% (55 patients) were male and 45% (45 patients) were female, indicating a slight male predominance.Among the patients, headache was the most common symptom, reported in 85% (85 patients), followed by seizures in 66% (66 patients). Weakness of the body was noted in 25% (25 patients), altered sensorium in 8% (8 patients), and other symptoms were present in 15% (15 patients).

Based on WHO grading, 100 tumor cases were analyzed. Grade 1 included 11 cases, with no IDH positivity or ATRX loss, 18.18% showing p53 positivity, and none with Ki-67 >5%. Grade 2 comprised 26 cases, of which 76.92% were IDH positive, 46.15% had ATRX loss, 61.54% were p53 positive, and 7.69% showed Ki-67 >5%. Grade 3 had 23 cases, with 56.52% IDH positivity, 34.78% ATRX loss, 86.96% p53 positivity, and 82.61% showing Ki-67 >5%. Grade 4 included 40 cases, with 35% IDH positivity, 27.5% ATRX loss, 45% p53 positivity, and all cases (100%) showing Ki-67 >5%. Overall, 54% of the cases were IDH positive, 34% had ATRX loss, 60% were p53 positive, and 69% showed a Ki-67 proliferation index greater than 5%. According to earlier research, high-grade gliomas with an IDH mutation had superior results. [12, 13] There is doubt regarding the prognostic significance of IDH mutations in low-grade glial tumors, although their relevance in high-grade gliomas is clearly established. IDH1-mutated DA has been shown to have a longer overall survival than IDH1 wild cases (150.9 vs. 60.1 months), according to Sun H et al. [12] A small number of further studies have indicated that individuals with Grade 2 IDH-mutant gliomas have a better prognosis. But in other research, patients with IDH mutant gliomas did not have better results. Diffuse gliomas are classified molecularly using ATRX status with IDH1/IDH2 mutation and 1p/19q co-deletion status, which is thought to be superior to standard classification. Consequently, tumors that have intact 1p/19q, an IDH mutation, and a loss of ATRX expression have been categorized as astrocytomas. IDH1 and ATRX status testing is necessary for all patients with diffuse gliomas since 1p/19q co-deletion and ATRX mutation are mutually exclusive.[13, 14] p53 IHC is employed as a highly specific marker for p53 mutational analysis

detection. P53 mutation is mutually exclusive 1p/19q co-deletion, and it is always linked to IDH1-R132H tumors in Grade 2 and Grade 3 malignancies. As a result, p53 is chosen for analysis and is a useful IHC marker. The significance of p53 and ATRX IHC without 1p/19q co-deletion mutational study is suggested by the high association between p53 mutation, which is mutually exclusive with 1p/19q co-deletion, and ATRX loss, which is likewise mutually exclusive with 1p/19q co-deletion. [24, 25] The presence of a p53 mutation in low-grade gliomas is indicative of aggressive tumor activity, which typically manifests 3-6 years after diagnosis because this is the amount of time needed for the p53 mutation to propagate, as evidenced by widespread p53 positive in recurrences.[15, 16]

A higher level of Ki-67 expression is linked to a worse prognosis and is a measure of the proliferation of cancer cells. High levels of Ki-67 antibodies are found in high-grade gliomas. The most prevalent symptom in patients with low-grade gliomas, poor seizure control rate, is linked to high Ki-67 expression in 19.4% of cases. The Ki-67 indices of gliomas of similar grade were comparable. Ki-67 antibody is helpful for both low- and high-grade gliomas, however it might be challenging to classify and distinguish between grades. Ki-67 is therefore regarded as a tumor-grade marker in conjunction with other IHC markers and histomorphological characteristics rather than by itself. [17, 18]

Based on histological subtypes, Low-grade tumors like PA and GG showed no IDH positivity or ATRX loss, while DA and AA had moderate to high expression of IDH, ATRX loss, and P53, with increased Ki-67 in AA. P GBM had low IDH and ATRX but high Ki-67 (100%), whereas S GBM showed high IDH, ATRX loss, P53, and Ki-67. ODG had high IDH positivity, moderate P53, and no ATRX loss or Ki-67 elevation, indicating a distinct profile. Cai J et al.[19] conducted a study in which they discovered that there was little difference in survival between IDH mutants DA and AA. Astrocytic lineage frequently has ATRX mutations. To ascertain nuclear ATRX expression, IHC is utilized. It mostly affects astrocytic lineage gliomas in Grades 2 and 3, or DA and AA. ODG and primary glioblastoma multiforme (GBM) both have it seldom. In a study involving 301 GBM patients, Garret M et al. [20] discovered that patients with an IDH1 mutation had improved overall and progression-free survival. Only a small number of studies have shown a connection between GBM patients' OS and abnormal expression of the ATRX, p53, and IDH1 proteins. To confirm the diagnosis in ODG patients with negative IDH1, 1p/19q co-deletion by fluorescence in situ hybridization (FISH) is required; if p53 is positive, this indicates a poor prognosis for these individuals. Grade 2 individuals are classified as having oligodendrogliomas if they have an IDH mutation, 1p/19q co-deletion, and retained ATRX. FISH subjects instances with ODG morphology and ATRX loss or astrocytic morphology and retained ATRX to 1p/19q co-deletion status.[21,22]

CONCLUSION:

Low Grades 1 and 2 gliomas with DAs, oligodendroglioma, and pilocytic astrocytoma were predicted to have the greatest prognosis by molecular IHC characterisation using immunomarkers IDH1-R132H, ATRX, p53, and Ki-67. The molecular group of AAs was predicted to have the worst outcome among glioblastoma patients. Combining IDH1 and ATRX IHC markers allows for an accurate determination of the molecular makeup of DA and AA cases, negating the need for expensive tests like FISH. p53 can function as a surrogate marker in astrocytic malignancies. In any case, our classification scheme can potentially accurately predict the molecular subgrouping of all glioma patients while also being unable to replace genetic analysis. Further evaluation and long-term follow-up are necessary to solidify their association with survival and prognosis because our study has atypical expression.

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