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Expression of isocitrate dehydrogenase 1 and tumor protein 53 in high-grade glioma and its correlation with the outcome – A prospective study at a tertiary care center in India

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ABSTRACT

Background: Central nervous system tumors are the 10th most prevalent cause of mortality worldwide. The 2016 World Health Organization (WHO) classification of high grade gliomas (HGG) has identified Isocitrate dehydrogenase 1 (IDH 1) mutation as one of the primary molecular markers. Tumor protein 53 (p53) mutation is also closely associated with HGG. **Aims and Objectives:** The current study intended to ascertain the expression of IDH1 and P53 in patients with HGG and correlate that expression with clinical prognosis. **Materials and Methods:** The study included 34 patients with histopathological proven HGG. Relevant clinical information was recorded. The immunostaining results with anti-mouse monoclonal antibody for IDH 1 (R132H) and rabbit polyclonal antibody for p53 (RP 106-05) were statistically analyzed. Patients were followed up through telephone for a period of 1 year. Mortality within 1 year was regarded as a poor outcome. **Results**: About 85.29% (29/34) of the patients had Grade IV glioma, while only 14.71% (5/34) had Grade III glioma. Most patients with Grade III (3/5) (60.00%) and Grade IV (21/29) (72.41%) gliomas had p53 positivity. The majority of the patients with grade-III glioma (3/5) (60.00%) had IDH1 positivity, while most of the patients (23/29) (79.31%) with Grade IV gliomas had IDH1 negativity (P = 0.0658). Age, gender, WHO grade, and adjuvant therapy did not show significant association with the outcome except for the p53 expression (P = 0.0011*) and IDH1 expression (P = 0.0025*). Correlation analysis showed a significant positive correlation between p53 makers with poor outcome (r = 0.4781) and glioma grade (r = 0.4028). Further, a negative yet insignificant correlation was recorded between IDH1 with age (r = −0.2285), p53 expression (r = −0.2568), and grade (r = −0.2988), although it showed a significant correlation with poor outcome (P = 0.0001). **Conclusion**: p53-positive and IDH1-negative HGG had a significant correlation with the poor outcome. Thus, IDH1 and p53 are reliable markers for prognostication of HGG.

Key words: Tumor protein 53; Glioblastoma multiforme; High grade glioma; Isocitrate dehydrogenase 1; Outcome

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INTRODUCTION

Brain and other central nervous system (CNS) cancers significantly cause mortality worldwide. In 2018, the global age-adjusted incidence rate of primary malignant CNS tumors was 3.5 cases per 100,000 population.[1] In India, CNS tumors accounted for 2.4% of all newly diagnosed cancer cases and 3.1% of cancer-related deaths in the same year. Males are more susceptible to malignant brain tumors than females.[2,3] Gliomas comprise approximately 75% of all primary CNS cancers, with the majority being diffuse gliomas. High-grade gliomas (HGG) are aggressive tumors with varying responses

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to treatment and a median survival ranging from 1 to 2 years.[4] The World Health Organization (WHO) 2016 classification of CNS tumors is based on molecular and phenotypic characteristics, aiming to identify prognostic factors and therapeutic targets. Key molecular markers identified in the new classification of HGG include isocitrate dehydrogenase 1 (IDH1) mutation, 1p/19q codeletion, and ATRX mutation. Tumor protein 53 (TP53) mutation, assessed through immunohistochemistry, is closely associated with 1p/19q co-deletion. TP53 mutations are linked to poor prognosis, treatment resistance, and metastasis in various cancers. IDH mutation is a valuable prognostic marker in gliomas.[5,6] In patients with glioblastoma multiforme (GBM), those with IDH1 mutation have a median survival of around 31 months, compared to 15 months in patients with wild-type IDH1.[7] Understanding the factors that contribute to better prognosis in these patients may lead to improved management strategies. This study aims to determine the expression of IDH1 and P53 in high-grade glial tumors in patients from Uttar Pradesh and correlate their expression with patient outcomes. This research could provide a foundation for potential targeted therapies in the future.

Aims and objectives

1) To determine immunohistochemical expression of IDH1 and p53 in high grade glioma.
2) To analyze the correlation between expression of IDH1 and p53 with outcome in terms of mortality in high grade glioma patients.
3) To seek association between expression of IDH1 & p53 with clinicopathological parameters like age, gender, histological grade.

MATERIALS AND METHODS

This study was approved by the Institutional Ethical Committee of Integral Institute of Medical Sciences and Research (IIMS&R) and King George's Medical University (KGMU), Lucknow, vide IEC/IIMS&R/2021/49 and ECR/262/Inst/UP/2013/RR-19, respectively. This prospective observational study was conducted at the Department of Pathology, IIMS&R, Lucknow, from March 2021 to September 2022. Tissue biopsies of glial tumors were received postoperatively in 10% formalin from the Neurosurgery Department of KGMU.

Tissue samples of patients with histopathologically proven HGG (Grade III and IV) according to the WHO 2016 criteria were included in this study. Samples of patients with recurrent HGG who have already received chemotherapy and radiotherapy were excluded from the study. A total of 47 tissue samples were received and out of them, 34 samples on histopathological examination showed features of HGG and were included in the study.

Relevant clinical details were noted. For the histopathological study, specimens were fixed, grossed, processed, and paraffin-embedded. Sections of 3–5 microns were taken, stained with hematoxylin and eosin, and studied under a light microscope. All the biopsies diagnosed as glial tumor on routine light microscopy were graded as per criteria laid down by the WHO (2016). Additional sections of 3–5 microns thickness were taken; immunostaining was performed using anti-mouse monoclonal antibody for IDH 1 (R132H) and rabbit polyclonal antibody for p53 (RP 106-05) (Figure 1).

Interpretation and scoring system was as follows: IDH1 – cytoplasmic staining was taken as positive. The staining was evaluated according to the percentage of positive cells. The percentage of cells staining for IDH1 was scored as follows: (1) 10% of cells with cytoplasmic staining: positive and (2) <10% of cells with staining: negative. In the case of p53, nuclear staining was taken as positive. p53 was scored using a four-tiered scale: (1) <10% of nuclei stained(-), (2) 10–30% of the nuclei stained (1+), (3) 30.1–50% of the nuclei stained (2+), and (4)>50 % of the nuclei stained (3+). 2+ and 3+ were regarded as positive.

Patients in the study were followed up telephonically over a period of 1 year and details of adjuvant chemotherapy, radiotherapy, and survival were noted.

Outcome was determined on the basis of mortality. Mortality within 1 year of surgical management was taken as a poor outcome.

Statistical analysis

Data were entered in Microsoft Excel and analyzed using statistical software SPSS version 26 (SPSS Inc., Chicago, IL, USA). The continuous variables were evaluated by mean (standard deviation) or range value when required. The dichotomous variables were presented in number/

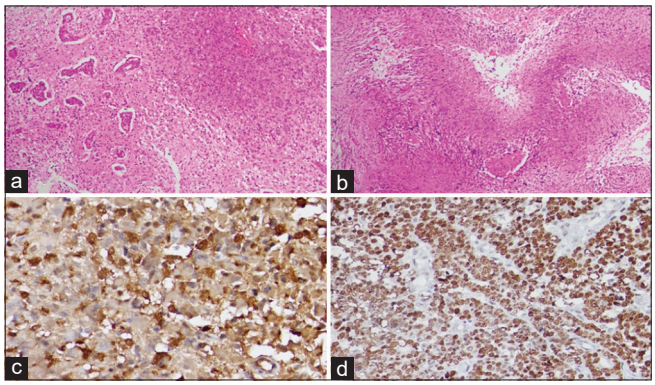

Figure 1: (a) Glioblastoma, Vascular endothelial proliferation (H and E, ×40), (b) Glioblastoma, Palisading of viable cells around a foci of necrotic area (H and E, ×40), (c) Glioblastoma, Isocitrate dehydrogenase 1 Positive (immunohistochemistry [IHC], ×400), (d) Glioblastoma, p53 Positive (IHC, ×400)

Table 1: Clinicodemographic parameters and adjuvant treatment of enrolled patients (n=34)

Clinicodemographic parameters	Grade-III (n=5)		Grade-IV (n=29)		P-value
	n	%	n	%	
Age (years)					
<18	0	0.00	1	3.45	χ^2=12.74
18–30	0	0.00	3	10.34	P=0.0259
31–40	0	0.00	8	27.59	
41–50	4	80.00	4	13.79	
51–60	0	0.00	11	37.93	
61–70	1	20.00	2	6.90	
Gender					
Female	3	60.00	08	27.59	χ^2=1.987
Male	2	40.00	21	72.41	P=0.1586
Histopathological diagnosis					
Anaplastic astrocytoma	5	100.00	0	0.00	χ^2=34.00
Glioblastoma multiform	0	0.00	27	93.10	P<0.0001*
Giant cell glioblastoma	0	0.00	2	6.90	
Adjuvant chemotherapy/radiotherapy					
No	4	80.00	20	68.97	χ^2=0.2501
Yes	1	20.00	9	31.03	P=0.6170

*P<0.05

Table 2: Survival time of the deceased HGG patients

Period of survival	Dead (n=31)		P-value
	n	%	
3 months	20	64.52	χ^2=10.76
3–6 months	4	12.90	P=0.0131*
6–9 months	5	16.13	
9–12 months	2	6.45	

HGG: High-grade glioma, *P<0.05

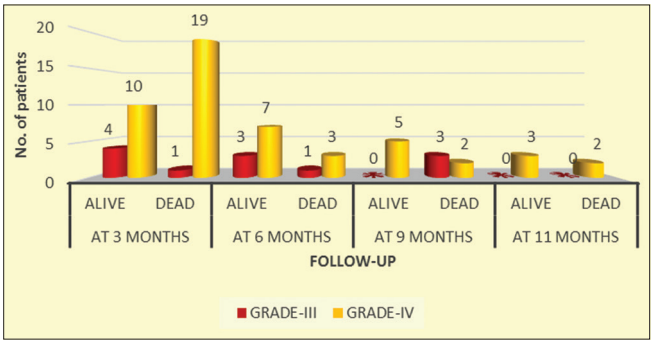

Figure 2: Outcome of enrolled patients having Grade III and IV glioma

frequency and were analyzed using Chi-square. To compare the means between the two groups, analysis by Student t-test was used. Correlation analysis was done using Spearman r correlation. At 95% confidence interval (CI), a P<0.05 or 0.001 was considered significant.

RESULTS

Out of 34 enrolled patients, 85.29% (29) had Grade IV glioma, while only 14.71% (5) had Grade III glioma. Grade III glioma patients were predominantly female (60.00%), whereas Grade IV glioma patients were mostly male (72.41%). The age distribution showed that 80% of Grade III glioma patients were between 41 and 50 years, while Grade IV glioma patients were primarily in the 31–60 age range (Table 1). Histopathological diagnosis revealed that all Grade III glioma patients had anaplastic astrocytoma, while most Grade IV glioma patients had GBM (93.10%) (Table 1).

Most patients had not received any chemotherapy or radiotherapy either due to financial or family/logistical issues (Table 1). Unfortunately, all grade III glioma patients died within the follow-up period of 1 year while only three grade IV glioma patients survived at the end of the follow-up period of the study. About 64.52% (20) patients died within 3 months (Table 2 and Figure 2).

Statistically, a non-significant difference was observed in the outcome of the enrolled patient among Grade III glioma and Grade IV glioma groups (Table 3).

Most patients with both Grade III (60.00%) and Grade IV (72.41%) gliomas exhibited p53 positivity. Grade III glioma (60%) patients had positive IDH1 expression, whereas Grade IV glioma (79.31%) patients had negative IDH1 expression (Table 4).

The outcomes of the enrolled patients did not show significant associations with age, gender, histopathological diagnosis, WHO grade, and adjuvant chemotherapy/radiotherapy except for p53 expression (P=0.0011*) and IDH1 expression (P=0.0025*) (Table 5).

Table 3: Outcome of the enrolled patients having high-grade glioma

Outcome	Grade-III (n=5)	Grade-IV (n=29)	Log-rank (Mantel-Cox) test
Number of rows	34	34	
#Deaths/Events	5	26	df=1
Median survival	180	63	χ^2=0.5170 P=0.4721
	Hazard ratio (Mantel-Haenszel)		
	Grade III/Grade IV	Grade IV/Grade III	
Risk ratio	0.5003	1.999	
95% CI of ratio	0.2105–1.189	0.8409–4.751	

CI: Confidence interval

Table 4: Expression of p53 and IDH1 in HGG patients

Markers	Grade-III (n=5)		Grade-IV (n=29)		P-value
	n	%	n	%	
p53					
Positive	3	60.00	21	72.41	χ^2=0.3166
Negative	2	40.00	8	27.58	P=0.5737
IDH1					
Positive	3	60.00	6	20.69	χ^2=3.386
Negative	2	40.00	23	79.31	P=0.0658

IDH1: Isocitrate dehydrogenase 1, HGG: High-grade glioma

Positive p53 expression and negative IDH1 expression correlated with poor outcome. Correlation analysis showed a significant positive correlation between p53 makers with outcome (P=0.0004*; r=0.4781) and glioma grade (P=0.0182*; r=0.4028). Further, correlation analysis showed a negative yet insignificant correlation between IDH1 with age (P=0.1937; r=−0.2285), p53 expression (P=0.1427; r=−0.2568), and grade (P=0.0860; r=−0.2988), except for outcome (P=0.0001*; r=−0.5985) (Table 6, Figures 3 and 4).

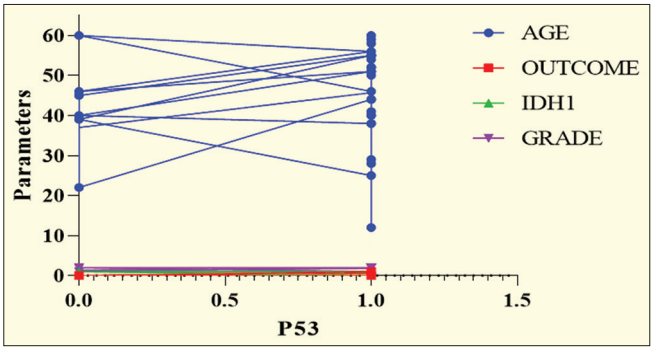

Figure 3: Correlation of p53 marker with other parameters in enrolled patients having grade III and IV gliomas

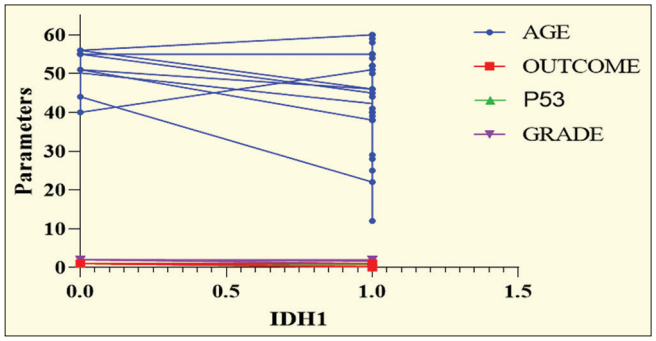

Figure 4: Correlation of isocitrate dehydrogenase 1 marker with other parameters in enrolled patients having Grade III and IV gliomas

DISCUSSION

The study observed that 80% of Grade 3 glioma cases were present in the age group of 41–50 while 37.93% of Grade 4 glioma cases were in the age group of 51–60. These findings were consistent with previous research conducted by Jalali and Datta,[8] Rasmussen et al.,[9] and Anand et al.[10] The median age in this study was 44 years which was similar to Ayad et al.,[11] and Ang et al.[12] Males had a higher incidence of HGG than females with a male-to-female ratio of 2:1, consistent with other studies.[13] The most prevalent histopathological subtype of HGG was glioblastoma (GBM) and its variants accounting for most cases (82.76%). Similar findings were reported by Singh et al.,[14] and Oslobanu and Florian.[15] Headache was the most common presenting symptom of glioma in this study followed by seizures which was consistent with the study of Mondal et al.,[16] and Singh et al.[14]

The comparison of WHO grade and the distribution of gliomas revealed that Grade IV was more prevalent than Grade III in this study which is consistent with the findings of Ayad et al.[11] In our study of 34 cases of HGG, Grade III comprised 14.7% of cases while Grade IV were 85.29%. At the same time, Ang et al.,[12] found that 31% of cases were in the Grade III group while 69% were in the Grade IV group.

In our study, 24 out of 34 cases (70.59%) showed immunoreactivity for p53. Three out of five cases (60.00%) were positive in Grade III gliomas cases. In the Grade IV group, 21 out of 29 cases exhibited positive p53 expression (72.41% positivity). Statistically, a non-significant difference was noted in p53 positivity among groups (P=0.5737). This was in accordance with Hu et al.,[17] Further Jin et al.,[18] found that 63.8% of cases showed immunopositivity for p53. In a study of 60 cases entailing normal brain tissue, gliosis, and

Table 5: Association of the outcomes with various parameters of enrolled HGG patients

Clinicopathological parameters	Outcome				P-value
	Alive (n=3)		Dead (n=31)		
	n/Mean	%/SD	n/Mean	%/SD	
Age (years)					
<18	0	0.00	0	0.00	χ^2=4.996
18–30	0	0.00	3	9.68	P=0.2877
31–40	0	0.00	8	25.81	
41–50	0	0.00	8	25.81	
51–60	2	66.67	10	32.26	
61–70	1	33.33	2	6.45	
Mean±SD	44.00	22.99	46.32	10.71	t=0.3236 P=0.7483
Gender					
Male	1	33.33	10	32.26	χ^2=0.001445
Female	2	66.67	21	67.74	P=0.9697
Histopathological diagnosis					
Anaplastic astrocytoma	0	0.00	5	16.13	χ^2=0.2479
Glioblastoma multiform	3	100.00	24	77.42	P=0.6186
Giant cell glioblastoma	0	0.00	2	6.45	
Adjuvant chemotherapy/radiotherapy					
No	3	100.00	21	67.74	χ^2=1.371
Yes	0	0.00	10	32.26	P=0.2416
Histopathological WHO grade					
Grade-III	0	0.00	5	16.13	X^2=0.5673
Grade-IV	3	100.00	26	83.87	P=0.4513
p53					
Positive	0	0.00	26	83.87	χ^2=10.69
Negative	3	100.00	5	16.13	P=0.0011*
IDH1					
Positive	3	100.00	6	19.35	χ^2=9.140
Negative	0	0.00	25	80.65	P=0.0025*

HGG: High-grade glioma, WHO: World Health Organization, IDH1: Isocitrate dehydrogenase 1, *P<0.05

Table 6: Correlation of p53 marker with other parameters in enrolled patients having Grade III and IV gliomas

Statistical tests	p53 versus Age	p53 versus outcome	p53 versus IDH1	p53 versus grade	IDH1 versus age	IDH1 versus outcome	IDH1 versus p53	IDH1 versus grade
Spearman r	0.2972	0.4781	−0.2568	0.4028	−0.2285	−0.5985	−0.2568	−0.2988
95% CI	−0.05595–0.5842	0.1355–0.7125	−0.5547–0.09944	0.06449–0.6581	−0.5335–0.1291	−0.7984–−0.1949	−0.5547–0.09944	−0.5854–0.05416
P-value	0.0879	0.0004*	0.1427	0.0182*	0.1937	0.0001*	0.1427	0.0860

IDH1: Isocitrate dehydrogenase 1, CI: Confidence interval

gliomas, Hussein et al.,[19] observed p53 expression in 50% of cases of grade III and 92% of cases of Grade IV gliomas.

In the present study, most Grade III glioma patients (60.00%) showed IDH1 expression while only 20.69% of cases of Grade IV glioma showed immunoreactivity for IDH1. Statistically, a non-significant difference was noted in IDH1 positivity among groups (P=0.658). The study by Ang et al.,[12] showed a higher percentage of IDH1 expression in Grade III glioma cases compared to grade IV (P=0.074).

In our study, only 3 (10.34%) HGG patients were alive at the end of the study. Three patients were still alive after the follow-up period of 12 months. The findings were similar to Noiphithak and Veerasarn.[20] In the study by Ayad et al.,[11] after a follow-up period of 2 years, 46.7% of patients were alive and 53.3% were dead. Skewed high mortality in our study was due to incomplete treatment of patients as the majority did not received adjuvant chemotherapy/radiotherapy. In the present study, most patients were dead at the follow-up period of 3 months after surgery (64.52%). The median survival was higher in patients with Grade III glioma (180 days) than those with Grade IV glioma (63 days). Further, the hazard risk ratio was higher in Grade IV glioma (1.999) than in Grade III glioma (0.5003). In addition, Smoll et al.,[21] found that the first quarter of the 2nd year (5th quarter) post-diagnosis showed the peak incidence of mortality with an excess

hazard ratio of 7.58 (95% CI=6.54, 8.78). Mladenovsk et al.,[22] in a study of 121 operated patients with HGG found that overall survival was 12.23 months. Median survival in patients with gross total resection was 14.53 months while patients with subtotal resection was 10.44 months. Mohammed et al.,[23] showed that 52.8% of patients above 40 years survived up to 1 year and 8.3% up to 2 years. Accordingly, Chansriwong and Sirisinha[24] reported that the overall survival time in patients with HGG was 604.04 days.

In our study, parameters such as age, gender, histopathological diagnosis, adjuvant treatment, and WHO grade of tumor did not show any association with outcome. However, Noiphithak and Veerasarn[20] and Chansriwong and Sirisinha[24] observed that radiotherapy influenced survival in patients of HGG. This difference may be due to the fact that most of the patients (grade III [80.00%] and grade IV [68.97%]) in our study have not received chemotherapy or radiotherapy. However, in our study, a significant association was noted between outcome and p53 expression (P=0.0011) and IDH1 expression (P=0.0025). On the contrary, Stancheva et al.,[25] found no significant difference in survival between mutated and non-mutated TP53 groups.

In our study, most of the patients who died had positive p53 and negative IDH expressions. A similar observation was made by Chaurasia et al.,[26] and they found that the patients with each IDH+ or p53 – GBM showed better survival than patients with counterpart protein-expressed GBMs. The present study recorded a significant positive correlation between p53 makers with outcome (P=0.0004*; r=0.4781) and glioma grade (P=0.0182*; r=0.4028). At the same time, a positive yet insignificant correlation was noted between p53 and age (P=0.0879; r=0.2972). A negative correlation between p53 and IDH1 (P=0.1427; r=−0.2568) was also noted in our study. Similar observations were made by Jin et al.,[18] in a meta-analysis of 21 studies including 1322 glioma patients found a positive relationship between p53 expression, glioma grade, and overall survival.

However, Birner et al.,[27] in a study of 220 cases of infiltrative low- and HGG found no association of p53 expression with histological grading (P>0.05). In the present study, a negative yet insignificant correlation between IDH1 with age (P=0.1937; r=−0.2285), p53 expression (P=0.1427; r=−0.2568), and grade (P=0.0860; r=−0.2988) was noted. However, there was a significant correlation with outcome (P=0.0007*; r=−0.5533). Similarly Lv et al.,[28] found that IDH1 mutation significantly correlated with a longer overall survival (OS) from the initial diagnosis. However, Birner et al.,[27] found no significant effect of IDH expression on survival in Grade III and IV gliomas separately (P>0.05). In a study by Takano et al.,[29] p53 expression was an independent prognostic factor for progression-free survival in Grade III gliomas.

Limitations of the study

First, the small sample size of the study is one of the limiting factors in the study. A larger sample size is required to confirm the encouraging results and prognostication. Second, high mortality in the early follow-up period due to incomplete treatment (non-receiving of adjuvant chemoradiation) hampers the actual overall survival period and hinders the prognostication value of the markers. Finally, the skewed sample size difference between Grade III and Grade IV glioma might also have an impact on the results.

CONCLUSION

Both p53 and IDH1 showed a significant correlation with the poor outcome. The maximum patient who died had p53-positive and IDH1-negative tumors. Thus, IDH1 negative and p53 positive can act as a reliable marker for poor prognosis. Therefore, individually and as a combination, these biomarkers can stratify HGG (Grade III and IV) into prognostically relevant subgroups and have strong prognostic values.

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