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Original Article

Clinicopathological Analysis of Glioma Patients: An Observational Retrospective Analysis from a Tertiary Level Hospital of Central India

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Abstract

Introduction: Gliomas are tumors of the glial cells, the most common primary malignant brain tumour in adults. Gliomas are difficult to treat, and the overall survival for patients with high-grade tumours is short. This study aims to conduct a clinicopathological features of gliomas to understand their characteristics, prevalence, and clinical outcome.

Methods: This retrospective descriptive clinicopathological study was conducted at the Department of Pathology, of rural tertiary care hospital of central India from 2018 to 2023. One hundred three cases of glioma specimens were received during this study period. Tumor slides were then reviewed by two pathologists. The age, sex, site, clinical presentation, diagnosis, World Health Organization grade, and the histological subtypes were recorded and then analysed using the SPSS version 27.0.

Results: Gliomas were highest in the age group of 30 to 50 years with mean age at diagnosis of 44.35 years. The most frequently reported symptom among present study patients was headache (31.07%, n=32), followed by seizures (26.22%, n=27). Glioblastoma (grade 4) was the most common subtype of glioma (44.66%). The frontal lobe and temporal lobe were the most common accounting for the location 24.27%, cases each. On histopathology majority of cases (44.6%) were glioblastoma followed by diffuse astrocytoma (26.21%)) and pilocytic astrocytoma (16.50%). A roughly inverse but statistically significant correlation was found between tumor size and survival outcome (P=0.0001). Gliomas with radiological tumor size less than 4 cm was associated with better prognosis and vice-versa. Histological grade of glioma has significant impact on survival outcome. High grade gliomas (grade 3 and 4) showed a higher mortality rate 40.77% (n=42/46) and a low survival rate 3.88% (n=4/46) than low grade glioma.

Conclusion: Of all gliomas, glioblastoma was the predominant histological subtype and associated with poor prognosis. The current study, sheds light on the rising burden of glioma in developing countries over the past decades, with a notable trend of the disease manifesting at younger ages.

Keywords: Glioma, Analysis, Glioblastoma, Subtypes, Clinical outcome

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Introduction

Central nervous system (CNS) neoplasms contribute approximately 1–2% of all the tumours and have variable morphological and differentiation characteristics, which leads to significant challenges.[1] Gliomas are the most common CNS tumours (40%) both in children, and adults characterize mainly by astrocytes or oligodendroglia differentiation.[1,2]

Gliomas are classified into different types, mainly astrocytoma, oligodendroglioma, diffuse glioma and glioblastoma (GBM).[2,3] The clinical features of a glioma patients can differ according to the site and stage of the tumor.[4,5] The typical symptoms are headache, convulsion, and progressive neurologic impairments, of which convulsion is the most common and observed in as many as 25% of patients.[2,4]

According to WHO (World Health Organization) 2016 classification glial tumors were classified as diffuse astrocytic and oligodendroglia tumors which included grade II, III, and grade IV glial tumors. These glial tumors were further sub classified on the basis of histology and molecular markers. WHO grade was determined based on histology. Other glial tumors included grade I glial tumors, namely, pilocytic astrocytoma. High grade gliomas (grade 3 and grade 4) are frequent histologic types of primary brain tumours than those of other primary brain tumors.[6,7]

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The majority of high-grade gliomas, lack curative treatment choices, though surgery followed by chemotherapy and radiation therapy is the most common treatment. Temozolomide is currently used to treat these tumors as it is capable of crossing the blood-brain barrier.

Despite all available adjunct treatment methods, the prognosis of glioma patients is worse with significant neurological deficit. The survival outcome of gliomas depends largely on histomorphology, along with age at presentation and biomarkers.[3]

Further, the treatment of gliomas in rural setup is impeded by growing financial burden, insufficient clinical investigations, and scarcity of even primary therapeutic agents. Also, limited number of neurosurgeons and paramedical staff create a large therapeutic gap for glioma patients in low -income countries like India. Due to lack of accessible surgical care, cases are referred to higher centres in big cities. CNS surgeries are mostly high-priced, and accessing good neurological care is out of the pocket of most of the rural people.[3,4]

Further, lack of proper diagnostic techniques often results in misdiagnosis of gliomas hence contributing to worse outcomes particularly in rural setup. Low resources for post-treatment radio-diagnosis, imaging and limited follow-up also contribute for tumor recurrence in these patients.

Most of the previous studies have focused on CNS tumors as a whole, herein, we have intended on only for histopathological diagnosed cases of glioma only so as to present an undiluted picture of prevalence glioma especially in developing countries like India.[4,5,6]

In spite the myriad of available data from the cancer registry, very few studies explore the epidemiology of brain cancers in the India. The incidence of brain tumors also varies significantly across different parts of India. These differences could be reflective of availability of investigative methods and therapeutic practices. Further, it is also essential to explored environmental and socio demographic characteristics to understand the etiopathogenesis of CNS tumors.[3,5,7]

Therefore, understanding the burden of these cases helps clinicians in the early detection and the management of gliomas. In the present study we aim to look at and frequency of glial tumors, its clinicopathological features and disease outcome in the rural population of India.

Methods

This is a retrospective non- interventional observational cohort study of gliomas conducted at histopathology section of pathology department, at tertiary level hospital of central India. 103 cases diagnosed and treated for glioma, at Neurosurgery unit from June 2018 to June 2023, was recovered from histopathology records and population-based cancer registry housed in the pathology department. The final diagnoses in all the 103 cases were made on histopathological sections of biopsy tissue. These 103 diagnosed cases of glioma were further reclassified according to the 2016 World Health Organization (WHO) classification. Detailed demographic and clinical details regarding patient age, gender, symptoms, radiological findings (tumor size), type of surgery, histopathological diagnosis, WHO grade, stage. Molecular markers such IDH1 mutation, MGMT and ATRX are important prognostic markers in the glioma. Due to limited resources and financial restrains molecular markers were not done in the present study.

We also searched for potential risk factors, such as exposure to ionizing and nonionizing radiation, allergic conditions, and chronic infections, immunologic, genetic, and developmental condition. We did not find any significant risk factors contributing to the pathogenesis of glial tumor in this study population.

For tumor size calculation Magnetic Resonance Imaging (MRI) measurements of two-dimensional (2D) diameters of the tumor through the imaging plane method was used.[8]

Representative pre-operative MRI quantitative measurements of tumor size was done by two neurosurgeons. Patients were followed up in Neurosurgery and radiotherapy OPD monthly for a period of 1 year for symptoms like paralysis, swelling at the operated site, recurrence of symptoms and complications of radiotherapy, as reported by their clinicians.

Patients who lost follow-up were approached on mobile phone to know disease outcome. Patients with incomplete follow up were already rejected from the study group. Patients with non-gliomatous tumours of the CNS were not included. Also, the cases with incomplete histopathological reports were excluded from the study.

Ethics committee clearance for data analysis was taken before preceding to study. Informed consent for utilisation of clinical and investigation reports for academic purpose of all the patients was taken at time of admission, as per routine institutional procedure.

Statistical Analysis

The proportion of glioma cases, clinical and histopathological features were analysed using Statistical Package for the Social Sciences (SPSS) version 27.0.A forward selection method is used to add variables. Disease outcome was analysed by the Kaplan-Meier survival curves and differences assessed by the stratified log-rank test. The results were considered as significant if the p value was < 0.05.

Results

In present study, mean age of patients was 44.35 ($\pm$ 16.02) years ranging from 7 years to 83 years. Seventy percent of patients were under 60 years. 13.59% (n = 14) were paediatric patients under 18 years of age whereas 31.06% (n = 32) patients were above 60 years of age. Thus, the large number of cases (n = 57) was from working age group of countries population (18–60 years), with peak prevalence in the third and fourth decades (55.33%). In our study, the prevalence of glioma was found more in males (54.37%) as compared to females (45.63%) with

male to female ratio of 1.24:1. There was a little or no difference in survival rate for females (3.38 ± 0.22 years) compared to males (3.57 ± 0.20 years).

The most frequently reported symptom among present study patients was headache (31.07%, n = 32), followed by seizures (26.22%, n = 27). Other clinical manifestations were, vomiting, mental confusion, /hemiparesis/para paresis/ weakness and altered sensorium. 26 (25.24%)

cases reported with mixed symptoms such as cognitive problems, vision changes, speech difficulties, etc. Regarding disease outcome in relation to symptoms, we noticed that, headache was associated with shorter life expectancy (2.33 ± 0.33 vs 3.74 ± 0.28 years.)

The symptoms had begun, in most cases, four weeks (62.50%) before they seek treatment. The patients who presented early to the hospital (< 4 weeks) had longer survival of 3.39 ± 0.36 years as compared to those who present late 1.72 ± 0.32 years.

Gliomas commonly involved cerebrum, of which frontal lobe and temporal lobe, were the favoured site contributing for 24.27% cases each. The parietal lobe is the second most common site involved by glioma accounting for 15.53% of the total cases. Whereas, cerebellar and brain stem tumours comprised of 17.47% and 11.65% cases respectively (Table 1).

On histopathology maximum number of cases (44.6%) were glioblastoma multiforme (n = 46), followed by diffuse astrocytoma (n = 27; 26.21%) and pilocytic astrocytoma (16.50%), in that order. Ependymoma and oligodendroglioma comprised 9.71% and 2.91% respectively (Figure 1).

Tumor size was a significant prognostic factor, and also determine risk of recurrence. On MRI, maximum tumor diameter is of 10–40 mm (n = 65; 63.1%) and the average volume of the tumor was 43.61 $cm.^3$ Maximum tumor diameter and the tumor volume were directly correlated with the survival outcome of patients ($P = 0.0001$). The tumor size, as measured in study, overall survival of patients was better with tumor size 2 -4cm (3.31 ± 0.25 years) than the patients with tumor size > 6 cm (1.14 ± 0.24 years) (Figure 2).

When we analysed our data, according to WHO 2016 grading of glioma, we found that 17(16.50%) belongs to WHO grade I, 22 (21.36%) belong to grade II, 18(17.48%) belong to grade III, and 46 (44.6%) belong to a grade IV. Histopathological features of glioma patients in the present study shown in Table 2.

Disease free survival of grade IV gliomas patients, for 3 months, 6 months, 12months and > 24 months was 10.68%, 3.88%, 9.71% and 3.88% respectively. While disease free survival for grade I glioma, at 12 months and 24 months was 1.94% and 12.62 % respectively (Figure 3). Likewise, grade IV gliomas has high mortality rate (42/46) and a low survival rate (4/46) at two year follow up period. On comparing the distribution of WHO grade with survival of patients, we found a significant difference ($P < 0.0001$) (Figure 4). Grade IV gliomas showed a high mortality rate 40.77% (n = 42/46). Table 3 shows survival outcome of grade of glial tumor, and a low survival rate

Table 1. Clinical parameters of glioma patients in the present study

Clinical parameters		Cases	Percentage
Gender	Male	57	54.37 %
	Female	46	45.63 %
Age (years)	1 – 18	14	13.59 %
	19-40	28	27.18 %
	41-50	29	28.16 %
	51-60	21	20.39 %
	61-70	7	6.80 %
	>70	4	3.88 %
Clinical features	Headache	32	31.07 %
	Vomiting	10	9.71 %
	Convulsion	27	26.21 %
	Hemiparesis/ Para paresis	16	15.53 %
	Altered sensorium	8	7.76 %
	Mixed	26	25.24 %
Duration of symptoms	<1 Week	15	14.56 %
	1 - 4 Week	32	31.06 %
	4 - 8 Week	24	23.30 %
	>8 Week	16	15.53 %
Location	Frontal	2 25	24.27 %
	Parietal	16	16.53 %
	Temporal	25	24.27 %
	Occipital	7	6.79 %
	Cerebellum	18	17.47 %
	Brain stem	12	11.65 %

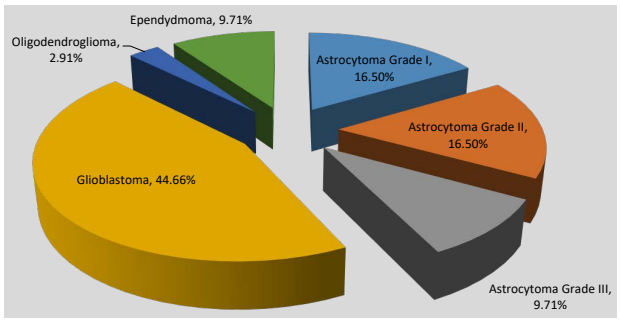


Figure 1. Distribution of Glioma cases according to the morphological subtype

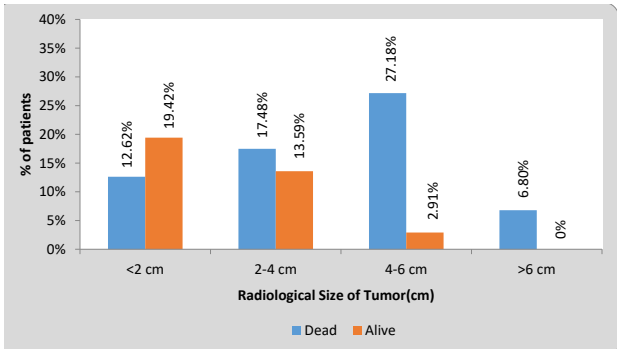


Figure 2. Survival outcome of glioma patients according to radiological size of tumor

3.88% (n=4/46). Table 4 presents the survival outcomes according to the grade of the glial tumor.

In terms of therapeutic management, complete surgical resection was performed in 57 (55.34%) cases and partial resection in 25 (24.28%) patients. Postoperative radiotherapy was received by 46 (44.66%) cases and chemotherapy in 47 (45.63%) cases with Temozolomide (TMZ).

The standard radiotherapy doses ranged from 54 Gy for low grade glioma to 60 Gy for high grade glioma at 1.8–2 Gy per fraction. Maximum number of patients (93.5%) were able to complete standard radiotherapy doses. Temozolomide (TMZ) was used for 2 to 7 courses after an operation 75 mg/m2 for 42 days, accompanied by monotherapy 150 mg/m2 for 5 days offered adjuvant CT.

Non-adherence to the treatment was the major reason behind poor outcome later in the disease course. 21/ 26 patients who had undergo surgery without radiotherapy and 19 /21 patients who received only radiotherapy without surgery were died of disease. In contrast 28/46

Table 2. Histopathological parameters of Glioma patients in the present study

Parameters		Cases	%	*P* value
Tumor size	<2 cm	33	32.04	
	2 - 4 cm	32	31.07	
	4 – 6 cm	31	30.10	
	>6 cm	7	6.80	
Microscopic findings	Nuclear atypia	86	83.50	
	Abnormal mitosis	61	59.22	
	Tumor Necrosis	44	42.72	
	Microvascular proliferation	10	9.71	
	calcification	8	7.77	
	Rossets	5	4.85	
WHO grade	Grade I	17	16.50	
	Grade II	22	21.36	
	Grade III	18	17.48	
	Grade IV (Glioblastoma)	46	44.66	
Treatment	Only Surgery	26	25.24	
	Only Radiotherapy	21	20.39	
	Surgery and radiotherapy	46	44.66	
	Surgery, radiotherapy and chemotherapy	10	9.71	
Recurrence at follow period of 6 months	Grade I	1	5.88	*P*=0.002 **S**
	Grade II	2	9.09	
	Grade III	9	50	
	Grade IV (Glioblastoma)	33	71.73	

Table 3. Survival outcome according to the grade of glial tumor

Grade of tumor	Dead	Alive	Total
Glioma Grade I	4(3.88%)	13(12.62%)	17(16.50%)
Glioma Grade II	7(6.79%)	15(14.56%)	22(21.36%)
Glioma Grade III	13(12.62%)	5(4.85%)	18(17.48%)
Glioma Grade (IV) Glioblastoma	42(40.77%)	4(3.88%)	46(44.66%)
Total	66(64.08%)	37(35.92%)	103(100%)
χ2-value	37.42, *P*-value=0.0001, Significant		

Note: [survival outcome according to grade of glial tumor; Dead or Alive (percentage of subgroup)].

Table 4. Means and Medians for Survival Time

Expression	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Grade 3 and 4	3.864	0.188	3.495	4.233	4.000	0.364	3.286	4.714
Grade 1 and 2	4.247	0.549	3.171	5.323	5.000	0.000	.	.
Overall	3.878	0.181	3.524	4.232	4.000	0.381	3.253	4.747

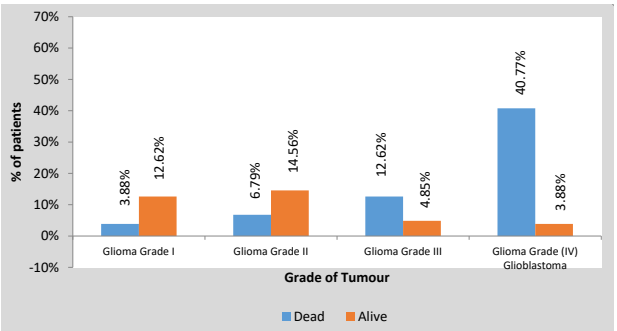


Figure 3. Survival outcome of glioma patients at the end of two years according to grade of tumor

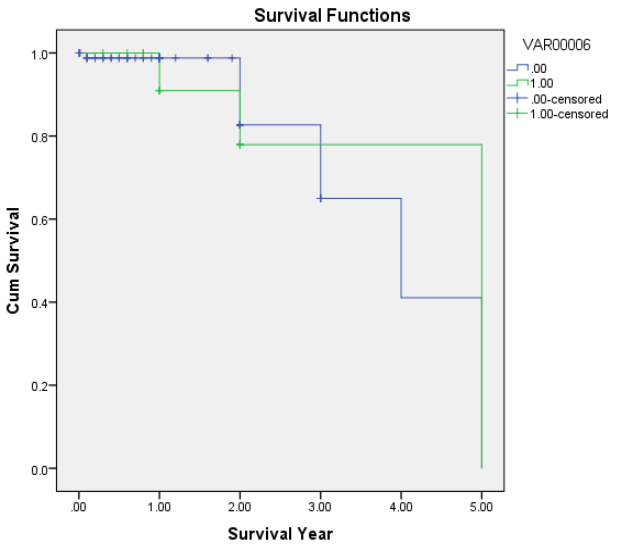


Figure 4. Kaplan Meier curve of survival outcome of glial tumours according to the histological grade [Low grade (grade 1, 2 - green line); high grade (grade 3,4 blue lines)]

patients who received complete treatment were alive. This indicate a statistically significant ($P = 0.0001$) correlation between survival outcome and compliance to the treatment.

Though, IHC offers valuable molecular insights into gliomas, clinicopathological analysis, even without IHC, plays a crucial role in understanding tumor behaviour, predicting prognosis, and guiding treatment strategies.

Discussion

Gliomas are the tumor derived from glial cells and most frequently encountered primary malignant brain tumor, constituting 38%–67% of brain tumors in different studies from India.[9,10,11] In recent years, the incidence of glioma has been sharply increasing worldwide, and has been attributed to better imaging and diagnostic technique.[11,12] Various predisposing conditions that have been contributed to the pathogenesis of gliomas, include, ionizing radiation, genetic syndromes, mobile phone usage, infections, dietary and occupational exposures.[10,12]

Gliomas showed marked variation with respect to age, gender, site, morphology, and disease outcomes. In present study, males (54.37%) outnumbered females (45.63%). In studies across the world showed male preponderance for the incidence of gliomas[12,13,14] In, Khan S et al study male cases outnumbered females for most histological subtypes of CNS tumours, maximum being recorded for glial tumours (321 male's vs 162 females).[12]

In the present study the mean age of gliomas at the time of diagnosis was 44.35 years. Khan S et al (2020) reported the median age of diagnosis of all brain tumors to be at 33.48 years.[12] While Ostrom et al. (2019) reported the median age of diagnosis of all primary brain tumors to be at 60 years.[15] We noticed that the mean age of gliomas patients was approximately a decade earlier than what is commonly reported in Western population.[15,16] The commonest presenting symptom were headache (31.07%) and convulsion (26.21 %), which was similar to the different studies from India and Western population.[16,17,18]

In our study population, supratentorial tumours predominate over infratentorial tumours. Maximum patients had tumours of the frontal and temporal region (24.27%), each followed by the parietal region (16%). Similar observation was made by Jaiswal et al. (2022) study in which the temporal lobe (35%) and the parietal lobe (25%) were commonly affected.[19] In present study most of the patients 31 % were presented within 4 weeks' duration of clinical manifestation. Fifteen (14.56%) patients seek medical attention within a week, while 24 (23.30%) cases came to the hospital around 8 weeks of duration of clinical manifestation. The finding was consistent with Decau M et al who noticed that most cases (62.50%) presented to hospital within a month of onset of symptoms.[20] However, Suresh SG et al found that the average duration from onset of symptoms to seek medical care was more than three months in about 40.3%.[21]

Liang J et al (2020) investigate the clinical characteristics and prognostic factors of 335 glioma patients. They found glioma was more common, with wide age range from 1year to 86 years. Convulsion was most common clinical complaint observed in 97 patients (29%).[2] Singh S et al (2021) analysed clinico- epidemiological profile 1450 operated cases of gliomas at tertiary care hospital. They noticed male preponderance (66.6%) with a mean age of 39.3 (± 17.36 SD) years. Most of the patients had grade 4 gliomas (41.4%) followed by diffuse astrocytoma (n = 331; 22.8%), pilocytic astrocytoma (6.2%) and oligodendroglioma (4.5%) in decreasing order.[3]

For high-grade glioma, standard treatment protocol was maximum safe resection of tumor along with adjuvant radiotherapy and temozolomide (TMZ). Adjuvant TMZ in the form of 6–12 cycles has been well established management in the past 10 years.[7,9,12,13,18]

Other chemotherapeutic drugs like lomustine, procarbazine, vincristine, bevacizumab etc are used, sometimes in combination. Bevacizumab is an anti-angiogenic drug, which targets vascular endothelial growth factor a protein that controls neo-angiogenesis. It also reduces oedema around the tumor, which can help alleviate neurological symptoms.[22]

As glioma is a fast growing tumor and occupying major portion of the brain parenchyma, safe surgical resection is strongly recommended. But as the brain parenchyma

is very sensitive, it is not always applicable to do such resection. Although, there is a strong evidence supporting, improved disease-free survival, better overall survival, and improved quality of life with greater extent of surgical resection.[23,24] In our study, safe surgical resection was not feasible and applicable in nearly half (44.66%) of the patients, while safe surgical resection was feasible in about quarter of our cases (25.24%). In 20.39% of the cases, only biopsy was performed as part of surgical intervention, for the reasons such as large tumor size, involving very crucial part of the brain parenchyma, tumours were deep within the parenchyma, comorbidities, and the poor general condition of patient. Similar findings were observed in Darwish et al.[24]

Regarding grade and histopathology, grade 4 (Glioblastoma) was making around (44.66%) of all patients in study, at the same time has main share in mortality among other histology. While, 76.47% grade 1 and 68.18 grade 2 glioma patient were alive at two years of follow up period ($P=0.0001$). Glioblastoma (grade 4) continues to have a poor prognosis. Advanced age, poor performance status, and incomplete extent of resection are all well-established negative prognostic factors.[24,25] However, Glioblastoma with molecular markers, such as isocitrate dehydrogenase 1 (IDH-1) and IDH-2 mutation and MGMT methylation, associated with good prognosis.[24] MGMT promoter methylation was identified as a prognostic and predictive marker for GBM patients treated with temozolomide. MGMT a mismatch repair enzyme, removes O6-methylguanine adducts induced by alkylator chemotherapies, thereby abolishing their cytotoxic effects. Therefore, high levels of MGMT was associated with temozolomide resistance. ATRX (alpha-thalassemia/mental retardation syndrome X-linked) mutations are commonly found in diffuse gliomas, particularly astrocytoma's and secondary glioblastomas, and are often associated with IDH mutations and TP53 mutations, while being mutually exclusive with 1p/19q codeletion.[22,25]

There is a need for proper counselling about the benefits of a completely non-invasive treatment modality like radiation for providing the best possible care to the patients. Multimodality treatment, which includes surgery, radiotherapy, and chemotherapy, is still the gold standard for treating primary brain tumours.

Though the study of molecular marker gives valuable insights into gliomas, clinicopathological analysis, even without IHC, still plays a pivotal role in understanding tumor behaviour, predicting prognosis, and guiding treatment strategies. By analysing pathological tumor grade, location, tumor size patient characteristics, and survival data, clinicians can make informed decisions about therapeutic management of glioma patients.

The other limitation of the study is small sample size. Also, this hospital-based study did not indicate the exact prevalence in the community. Therefore, analytical community based studies with prospective approach to monitor the incidence-trends, risk factors and diseases survival of patients with gliomas are required for better clinical outcome.

Conclusion

Gliomas were most common primary brain tumours. Glioma was most common in the 5th decade with no gender predilection. About three-quarters of the tumours were supratentorial. Headache and seizure were the common presentations. Of all, glioblastoma was the predominant histological type with worst prognosis The present study is one of the rare studies to be conducted on adequate number of patients (more than 100) diagnosed with glioma specimens. Additionally, our research shows rising burden of glioma in low economic countries over the past decade, with a notable trend of the disease affecting at younger ages.

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Writing–Review & Editing: Manisha A. Atram, Vijay Bhalavi

Competing Interests

None.

Ethical Approval

The study was rewieved and approved by Institutional ethics committee.

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