SCIENTIFIC ARTICLE

Predicting the risk of high-grade gliomas in resource-constrained settings

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Abstract

Introduction

Gliomas are the most common primary brain tumours worldwide and can be broadly classified as low-grade or high-grade based on molecular and histopathological features.

Methodology

A retrospective single-centre, single-surgeon, unmatched case-control study was conducted using sociodemographic, clinical, and radiological information available from the Asiri Central Brain Tumour Registry, including 36 patients histologically diagnosed with low-grade gliomas who presented to Asiri Central Hospital, Sri Lanka, between 2019 and 2022, and 36 patients with high-grade gliomas. Initial bivariate analysis was conducted using chi-square tests and Fisher's exact tests, followed by multivariate analysis using logistic regression to develop the final model.

Results

The mean age of the participants was 39.51 years (SD = 20.57 years), and the majority were males (n = 43, 59.37%). The initial bivariate analysis revealed that increased age (p = 0.004), hypertension (p = 0.005), dyslipidaemia (p = 0.042), total duration from symptom onset to presentation(p = 0.006) and contrast enhancement with IV gadolinium in MRI (p = 0.002) were significant factors for high-grade gliomas. The final logistic regression model identified male sex (p = 0.110, OR = 2.645), advanced age above 50 years(p = 0.014, OR = 5.217), speech deficit as a presenting complaint (p = 0.066, OR = 9.939) and contrast enhancement on MRI(p = 0.064, OR = 2.798) as predictors(Omnibus χ^2 (4) = 20.395, p < 0.001, R^2 = 0.247 (Cox & Snell), 0.329 (Negelkerke) as predictors for high-grade gliomas.

Conclusion

Sociodemographic and clinical characteristics combined with features of conventional MRIs can be utilized by clinicians to predict glioma grade preoperatively to plan and prepare treatment strategies.

Introduction

Among the primary brain tumours, gliomas predominate globally, with an age adjustment rate of 4.67 to 5.73 per 100,000 persons and an incidence rate of 6.5 per 100,000 people in the U.S. alone. [1,2] In the Sri Lankan context, the burden of central nervous system malignancies are described with age-standardized incidence rates ranging from 1.9 (females) to 2.5 (males) per 100,000 people. [3] However, specific details regarding the national statistics of gliomas are unclear, and research on this topic is scarce.

The tumour size, nodal status, and metastasis (TNM) system utilised in the pathological classification of systemic cancers is not applicable in the grading of gliomas or other brain and spinal malignancies in general since these lesions rarely metastasise outside the central nervous system (CNS). Hence, the World Health Organisation Classification of Brain Tumours utilises genomic data added to the morphological features of lesions to assess and predict the length of survival. Although still far from complete, the 5th edition of the WHO Classification of Tumours of the CNS published in 2021 builds upon its predecessors to establish different approaches for tumour diagnosis while highlighting the importance of layered reports. Accordingly, all gliomas are broadly graded into four schemas named using Arabic numerals 1 to 4. [4]

In contrast to the general belief on gliomas, low-grade gliomas (LGGs) (grades 1 and 2) account for 25% of all gliomas and carry an overall good prognosis. [1] On the other hand, high-grade gliomas (HGGs) (grades 3 and 4), such as glioblastoma, isocitrate dehydrogenase (IDH) wild type (grade 4) and astrocytoma, and IDH mutant (grade 3; previously designated as anaplastic astrocytoma), have an abysmal prognosis with high recurrence rates, short median lengths of survival and low success rates during surgical resection.[5]

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While definitive diagnoses of gliomas and their grades are molecular and histopathological, many studies have investigated the utilisation of different imaging modalities, such as T1 and T2 magnetic resonance imaging (MRI) techniques, MRI, functional MRI and even magneto encephalography, to differentiate LGGs from HGGs prior to surgery or biopsy, with varying outcomes. [6,7] However, few to no studies have attempted to compare patient presentations and demographics to identify risk factors for HGGs over LGGs to supplement radiology to arrive at a more specific collective diagnostic protocol. An attempt as such can aid clinicians in referring these patients for early surgery and help surgeons plan well in advance to achieve maximal resection and ensure favourable patient outcomes. Furthermore, this approach can be highly instrumental in lower economic countries where sensitive sophisticated imaging modalities are not readily available and human resources, particularly neurosurgeons, are lacking, giving rise to long waiting lists, nonavailability of theatre facilities and inequalities in geographical areas. Hence, clinical criteria can play a crucial role in providing radiological data for arriving at a more reliable combined clinical-radiological diagnosis.

Methodology

A retrospective single-centre single surgeon unmatched case-control study was conducted using information available from the Asiri Central Brain Tumour Registry (ACBTR). The ACBTR is an electronic database that contains socio demographic, clinical, radiological, histological, anaesthetic and follow-up data regarding patients undergoing surgery at the Asiri Brain and Spine Centre of the Asiri Central Hospital, Colombo, Sri Lanka. This study was conducted using detailed data from patients with a histological diagnosis of gliomas who underwent surgical resection from 2019 to 2022. Patients who were diagnosed histologically via biopsy but who had not undergone surgery, patients who had concurrent other brain tumours and patients with incomplete records were excluded from the study. Accordingly, 36 patients fulfilling the inclusion and exclusion criteria above with a diagnosis of LGGs were identified between 2019 and 2022. Thereafter, the first 36 patients with HGGs fulfilling the criteria included in the registry in the same period were selected as the unmatched patients. Then, information regarding sociodemographic factors, clinical presentations, examination findings, MRI findings prior to surgery and histological diagnosis was obtained from the same registry and rechecked by two separate investigators to address potential bias. Missing values were addressed, when possible, by missing data imputation based on the 10% missing value cut-off; otherwise, analysis was carried out based only on existing data. The data were analysed descriptively and analytically using IBM SPSS version 26.

Initial bivariate analysis was conducted for each of the individual factors using the chi-square test and Fisher's exact test when necessary. Dichotomisation of variables when necessary was performed according to expert opinions from a neurosurgeon, bioanalyst and histopathologist. Factors with $p < 0.2$ from the initial bivariate analysis underwent multivariate analysis using logistic regression to develop a model to identify the risk factors in patients considered to have gliomas. Ethical clearance was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Colombo, Sri Lanka.

Results

Study population

The ages of the patients included in the sample ranged from 3 to 78 years including 2 patients below the age of 18 years, with a mean age of 39.51 years (SD = 20.57 years), and the majority were males (n = 43, 59.37%). A larger proportion of the sample was younger than 51 years (n = 51, 70.8%).

Bivariate analysis

The initial bivariate analysis of clinical and socio demographic factors via χ^2 tests (and Fisher's exact test when necessary) identified several risk factors suggestive of high-grade gliomas, including sociodemographic characteristics such as age; health-related factors such as comorbid diabetes mellitus, hypertension and dyslipidaemia; past surgical-related factors such as past history of brain tumours; and factors related to clinical presentation, such as the presence of memory loss, headache, vertigo, vomiting, disturbances in speech and total duration from symptom onset to presentation. (**Table 1**) Certain other factors, such as history of allergies, history of alcohol and other substance use, and head trauma, did not appear to be significant even at $p = 0.2$.

Thereafter, the magnetic resonance imaging findings were subjected to bivariate analysis via χ^2 tests, which revealed that the presence of contrast enhancement with IV gadolinium was significantly associated with high-grade gliomas ($\chi^2 = 9.455$, $p = 0.002$; OR (95% CI = 4.6 (1.691-12.469)). (**Table 2**)

Multivariate analysis

Multivariate analysis using logistic regression and the backwards likelihood ratio method revealed that three sociodemographic/clinical factors, namely, male sex (OR = 2.957), advanced age above 50 years (OR = 6.825) and the

presence of speech disturbance as a presenting complaint (OR = 14.056), were associated with a greater risk of high-grade gliomas than low-grade gliomas. (χ^2 (3) = 16.937, $p < 0.01$) (**Table 3**).

Table 1: Clinical and sociodemographic predictors considered for regression analysis (n =72)

Predictor	Grade of Glioma		Total Number	Significance χ^2 *p* value
	Low-Grade Glioma N= 36 Frequency (%)	High-Grade Glioma N=36 Frequency (%)		
Age				
<50 years	31 (60.8)	20 (39.2)	51	***p* = 0.004**
≥ 50 years	5 (23.8)	16 (76.2)	21	
Diabetes Mellitus				
Absent	34 (54.0)	29 (46.0)	63	***p* = 0.075**
Present	2 (22.2)	7 (77.8)	9	
Hypertension				
Absent	33(58.9)	23(41.1)	56	*p* = 0.005
Present	3(18.8)	13(81.3)	16	
Dyslipidemia				
Absent	32(56.1)	25(43.9)	57	*p* = 0.042
Present	4(26.7)	11(73.3)	15	
History of Brain Tumours				
Absent	32(55.2)	26(44.8)	58	*p* = 0.074
Present	4(28.6)	10(71.4)	14	
Memory Loss				
Absent	29(54.7)	24(45.3)	53	*p* = 0.181
Present	7(36.8)	12(63.2)	19	
Headache				
Absent	16(41.0)	23(59.0)	39	*p* = 0.098
Present	20(60.6)	13(39.4)	33	
Vertigo				
Absent	32 (47.1)	36(52.9)	68	*p*= 0.115*
Present	4(100)	0(0)	4	
Vomiting				
Absent	29(46.8)	33(53.2)	62	*p* = 0.173
Present	7(70.0)	3(30.0)	10	
Speech Disturbance				
Absent	35(53.8)	30(46.2)	65	*p* = 0.107*
Present	1(14.3)	6(85.7)	7	
Total Duration of Symptoms (n = 39)	3(14.3)	18(85.7)	21	*p* = 0.006
Less than 3 months	10(55.6)	8(44.4)	18	
More than or equal to 3 months				

* Fisher's exact test was conducted

Final predictor model

To formulate a combined final predictor model with sociodemographic, clinical, and radiological factors, the three sociodemographic/clinical factors and the presence of contrast enhancement on MRI were considered together to formulate the final prediction model via multivariate analysis using logistic regression with the backwards likelihood ratio method, which yielded a sensitivity of 72.2%, specificity of 75.0% and a Negelkerke pseudo-R^2 of 0.329. An advanced age greater than 50 years (OR = 5.217), a speech deficit as a presenting complaint (OR = 9.939), contrast enhancement on MRI (OR = 2.798) ($p < 0.1$) and male sex (OR = 5.217) ($p < 0.2$) were identified. (**Table 4**) (χ^2 (4) = 20.395, $p < 0.01$)

Table 2: Association of radiological predictors with high grade gliomas (n =72)

Predictor	Grade of Glioma		Total Number	Significance χ^2 *p* value
	Low-Grade Glioma N= 36 Frequency (%)	High-Grade Glioma N=36 Frequency (%)		
Contrast Enhancement				
Present	13 (33.3%)	26 (66.7%)	39	$\chi^2 = 9.455$
Absent	23 (69.7%)	10 (30.3%)	33	***p* = 0.002**
Edema				
Present	8 (42.1%)	11 (57.9%)	19	$\chi^2 = 0.643$
Absent	28 (52.8%)	25 (47.2%)	53	$p = 0.422$
Hemorrhage				
Present	5 (45.5%)	6 (54.5%)	11	*$\chi^2 = 0.107$*
Absent	31 (50.8%)	30 (49.2%)	61	*$p = 0.743$*
Number of lobes involved				
More than 1 lobe	4 (36.4%)	7 (63.6%)	11	*$\chi^2 = 0.966$*
1 lobe	32 (52.5%)	29 (47.5%)	61	*$p = 0.326$*
Necrosis				
Present	1 (25.0%)	3 (75.0%)	4	*$\chi^2 = 1.059$*
Absent	35 (51.5%)	33 (48.5%)	68	*$p = 0.303$*
Tumour Boundary				
Unclear	7 (38.9%)	11 (61.1%)	18	*$\chi^2 = 1.185$*
Clear	29 (53.7%)	25 (46.3%)	54	*$p = 0.276$*

Table 3: Results of binary logistic regression analysis of clinical and sociodemographic factors (n=72)

Predictor	b	S.E.	*p*	Odds Ratio (OR)	90% C.I.	
					Lower	Upper
Age [a]						
> 50 years	1.921	0.651	**0.003**	6.825	2.341	19.908
Gender [b]						
Male	1.084	0.593	**0.068**	2.957	1.115	7.843
Speech Disturbance [c]						
Yes	2.643	1.214	**0.029**	14.056	1.909	103.495
Constant	-9.911	3.216	0.002	0.000		

Omnibus χ^2 (3) = 16.937, $p < 0.001$, $R^2 = 0.210$ (Cox & Snell), 0.279 (Negelkerke)

b = coefficient

S.E. = standard error of the coefficient

[a] Less than 51 years of age

[b] Female

[c] Absence of speech disturbance

Table 4: Final Binary Logistic Regression Model (n=72)

Predictor	b	S.E.	*p*	Odds Ratio (OR)	90% CI for OR	
					Lower	Upper
Age [a]						
>50 years	1.652	0.672	0.014	5.217	1.726	15.767
Gender [b]						
Male	0.972	0.608	0.110	2.645	0.973	7.191
Speech Disturbance [c]						
Present	2.296	1.247	0.066	9.939	1.278	77.276
Contrast Enhancement in MRI [d]						
Present	1.029	0.556	0.064	2.798	1.121	6.981
Constant	-1.772	0.603	0.003	0.170		

Omnibus χ^2 (4) = 20.395, $p < 0.001$, $R^2 = 0.247$
(Cox & Snell), 0.329 (Negelkerke)
b = coefficient
S.E. = standard error of the coefficient
[a] Less than 50 years of age
[b] Female
[c] Absence of speech disturbance
[d] Absence of contrast enhancement in MRI

Discussion

Gliomas are the most common type of primary tumour of the central nervous system and account for approximately 80% of all gliomas. Glioblastoma is the most common and most malignant form of glioma, accounting for 60% of all brain tumours in adults. Despite numerous advancements in surgery and oncology, glioblastoma and other high-grade gliomas are deadly, with median survival times ranging from months to several years. [8, 9, 10]

Why form a prediction model?

This is further aggravated by significant diagnostic delays that are associated with these high-grade gliomas, as evident from numerous studies conducted worldwide. A study conducted in the UK revealed that patients presenting with milder 'immediate nonthreatening' symptoms, such as episodic headache, depression, and personality changes, were more inclined to be reviewed for significantly longer durations due to the 'wait and see' approaches adopted or even misdiagnosis, which delays specialist referral. Even then, waiting lists for CTs and MRIs, the availability of hospital beds, and the requirement for repeat scans due to difficulties in discerning pathologies on radiology due to obscuration by oedema still prolong specialists from arriving at a diagnosis and definitive route of intervention. [11] Specifically, in cases such as Sri Lanka, where MRIs are not readily available in most hospitals, transfers between hospitals will take time, especially when consultant neurologists and neurosurgeons are unavailable at peripheral units, to hasten the process. However, there are discrepancies over the influence of time from the advent of clinical symptoms to first presentation to medical services, with different studies presenting different views on the topic. A retrospective study by Aggarwal et al. revealed that earlier diagnosis of glioblastoma was paradoxically associated with poorer operative survival, which was similar to what was observed in a study in the UK. [11,12,13] However, it must be noted that earlier presentations in their study were associated with older patients visiting emergency services, whereas patients with longer durations of diagnosis were largely composed of younger patients presenting to outpatient departments. These contrasting results could also be associated with the prevalence of neurological complaints being much lower than that at the time of definitive diagnosis. [14] In the present study, a shorter duration of symptom onset was significantly associated with a diagnosis of high-grade glioma according to the initial bivariate analysis ($p = 0.006$, OR [95% CI]: 7.500 [1.615-34.833]). This allies with the fact that a shorter duration of medical service could be due to more significant physical distress imposed on the patient by a more malignant fast-growing lesion than a relatively benign slow-growing low-grade glioma. However, due to the absence of definitive durations for a significant number of patients, multivariate analysis was not possible; hence, the significance of confounding could not be assessed after adjustment.

The influence of sociodemographic factors on HGGs

When considering the sociodemographic predictors identified in the present study, older age and male sex were consistent according to both the bivariate and multivariate analyses. This finding is in general agreement with the literature, where grade 3 gliomas (earlier widely known as anaplastic astrocytoma) had an average age of onset of 40 years, as opposed to glioblastoma, which had peak incidences between the ages of 65 and 74 years. [8,15] In contrast, the mean age of patients at diagnosis with LGGs was as young as 39.4 years (40 years in Caucasians and 34 years in African Americans). [1] This finding is in accordance with the widely accepted theories of the accumulation of mutations and the influence of ageing- and exposure-dependent changes on the tissue landscape, which influence tolerance at the cellular level to combat oncogenic mutations. [16] The cut-off of 50 years during dichotomisation in the present study was established after close review of these findings after a consensus was reached between a biostatistician and two neurosurgeons, whose findings were relevant to the current context. Male sex was consistently considered a risk factor for glioblastoma and other HGGs, with a male-to-female ratio of

1.5:1, which was not the case for LGGs where there was no sex predisposition. [17,18] Notably, other risk factors, such as geographic and ethnic variability, exposure to ionising radiation and the presence of hereditary syndromes, which were consistently found in the literature, were either not significant (such as ethnicity) or not assessed due to inapplicability (no patients were recorded with significant exposure to occupational or environmental exposure to ionising radiation or hereditary syndromes). [8,19,20] However, certain other factors, such as allergic history, alcohol consumption, smoking and tobacco history, history of trauma and head injury, which had conflicting results, were not significant predictors of high-grade gliomas in the present study. [8,21-25]

Clinical characteristics and HGGs

When considering the various aspects of medical history and comorbidities, past personal and family history of brain tumours and other cancers were considered significant risk factors for gliomas, with one study by Teppo et al. (2001) showing that overall brain tumour incidence was more than 3 times more common among people with lung carcinomas.[26] However, in 1997, an American case-control study revealed that even though a personal history of cancer or brain tumours was not significantly associated with the current risk for HGGs or LGGs, a family history of brain tumours may play a role in adult gliomas. [27] However, brain tumours, particularly glioblastoma, are well known for their high recurrence rate, with local recurrence patterns observed in as many as 79% of patients. [27] Thus, a past history of brain tumours (irrespective of the histological type or grade) identified as a significant predictor in the bivariate analysis of the current study (p = 0.074, OR [95% CI] = 3.077 [0.864 – 10.954]) could be valid.

Medical comorbidities such as diabetes, hypertension and hypercholesterolemia have long been debated as possible risk factors for high-grade gliomas, with conflicting evidence (evident from the present study where all three were significant in the bivariate analysis but none appeared after adjustment for confounding). [28,29] This finding is in accordance with the findings of a systematic review and meta-analysis regarding the association between diabetes and gliomas where conflict persists; diabetes is considered to have a protective effect on gliomas in case-control studies (OR = 0.68; 95% CI, 0.53–0.87; P = 0.002), and no significant association was identified in cohort studies (OR = 0.97; 95% CI, 0.83–1.13; P = 0.70). [30] This is representative of the fact that medical comorbidities while being significant in HGGs during bivariate analysis is actually masked by age where advanced age is coexistent in patients with higher medical comorbidities as well as HGGs.

There is a wide range of clinical presentations of LGGs and HGGs, with significant overlap between seizures and headaches accounting for 65-95% and 40%, respectively, of the cases of LGGs owing to their slow growth rate, which is an average of 4.1 mm/yr. [31] However, HGGs are nonspecific and can be caused by direct necrosis of brain tissue; secondary effects from increased intracranial pressure or location, manifesting as headache, nausea and vomiting, visual disturbances, and drowsiness; or, in the last case, seizures in 20-40% of HGGs. Visual, speech and other focal neurological deficits due to direct effects also constitute a significant proportion of presentations and could be more specific to HGGs than LGGs since they are more likely to induce necrosis owing to their rapid infiltration and growth. [10,32,33,34] This is also evident in the present study, where features of increased intracranial pressure, such as headache, vomiting, and vertigo, were significant in the initial bivariate analysis, and speech disturbance as a focal neurological deficit was seen as a predictor of HGGs in both bivariate and multivariate analyses.

Use of MRI for HGG detection in resource-constrained settings

Irrespective of sociodemographic factors and clinical presentations, radiological investigations led by MRI play a crucial role in preoperative diagnosis due to its superior soft tissue delineation and multiplanar capabilities. Mass effects, oedema, haemorrhage, necrosis and contrast enhancement under gadolinium resonance imaging (GGE) observed via conventional MRI are used as features for grading gliomas, with success rates varying from 55% to 83.3%. [35,36] However, these properties are not always reliable for tumour grading; for example, certain studies have shown that 40% of HGGs exhibit nonenhancement, while some LGGs exhibit avid enhancement. [36,39] This is evident from the findings of this study, where contrast enhancement was the only MRI characteristic that was significant according to bivariate analysis (χ^2 = 9.455, p = 0.002, OR [95% CI] = 4.600 [1.697 – 12.469]) and persisted to become a predictor of HGGs in the final regression model. These findings are comparable to those of a Chinese study in which preoperative MRI

characteristics were evaluated, in which rim enhancement was found to be the only significant feature in the final predictor model. [40] Their model, which also incorporated apparent diffusion coefficients (ADCs) from diffusion weighted imaging, had a sensitivity and specificity of 91.2% and 78.6%, respectively, which are comparable to the present model values of 72.2% and 75.0%, respectively.

Limitations

This study has several limitations, including (1) the absence of matching between cases and controls, (2) data collection limited to retrospective information, (3) observer variability in MRI characteristics, (4) the testing of 17 predictors with 36 events, which exceeded the 10 events per predictor rule of thumb, and (5) absence of molecular profiling data. However, as a single-centre single-surgeon study, observer variability regarding clinical assessments of patients was limited.

While this study did not attempt to differentiate between gliomas and other brain tumours, the current model can be utilized as a cornerstone to promote the utilization of clinicoradiological data for treating physicians to differentiate between different brain tumours before patients are referred for biopsy or surgery.

Conclusion

In conclusion, our study was conducted with the intention of building a simple prediction model based on clinical and basic radiological characteristics to aid clinicians in preoperative glioma grading. We have limited our ability to data that can be readily accessed by clinicians to avoid diagnostic delays attributed to experimental or sophisticated imaging modalities, especially in the context of resource-poor settings where conventional MRIs play a crucial role in diagnosis and treatment. Furthermore, we have attempted to transcend traditional imaging-based models to incorporate clinical characteristics to improve accuracy, prioritising patient-focused diagnosis.

Ethical approval

Ethics Review Committee of the Faculty of Medicine, University of Colombo, Sri Lanka approved this study (Ethics Review Committee Reference Number: ERC/23/117).

Institution of reference

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