Seizure Burden and Clinical Risk Factors in Glioma-Related Epilepsy: Insights From MRI Voxel-Based Lesion-Symptom Mapping

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Background: Epilepsy is the most common preoperative symptom in patients with supratentorial gliomas. Identifying tumor locations and clinical factors associated with preoperative epilepsy is important for understanding seizure risk.
Purpose: To investigate the key brain areas and risk factors associated with preoperative seizures in glioma patients.
Study Type: Retrospective.
Population: A total of 735 patients with primary diffuse supratentorial gliomas (372 low grade; 363 high grade) with preoperative MRI and pathology data.
Field Strength/Sequence: Axial T2-weighted fast spin-echo sequence at 3.0 T.
Assessment: Seizure burden was defined as the number of preoperative seizures within 6 months. Tumor and high-signal edema areas on T2 images were considered involved regions. A voxel-based lesion-symptom mapping analysis was used to identify voxels associated with seizure burden. The involvement of peak voxels (those most associated with seizure burden) and clinical factors were assessed as risk factors for preoperative seizure.
Statistical Tests: Univariable and multivariable binary and ordinal logistic regression analyses and chi-square tests were performed, with results reported as odds ratios (ORs) and 95% confidence intervals. A *P*-value <0.05 was considered significant.
Results: A total of 448 patients experienced preoperative seizures. Significant seizure burden-related voxels were located in the right hippocampus and left insular cortex (based on 1000 permutation tests), with significant differences observed in both low- and high-grade tumors. Tumor involvement in the peak voxel region was an independent risk factor for an increased burden of preoperative seizures (OR = 6.98). Additionally, multivariable binary logistic regression results indicated that 1p/19q codeletion (OR = 1.51), intermediate tumor volume (24.299–97.066 cm^3), and involvement of the peak voxel (OR = 6.06) were independent risk factors for preoperative glioma-related epilepsy.
Conclusion: Voxel areas identified through voxel-based lesion-symptom mapping analysis, along with clinical factors, show associations with clinical seizure burden, offering insights for assessing seizure burden for glioma patients.
Level of Evidence: 4
Technical Efficacy: Stage 1

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Gliomas are highly epileptogenic central nervous system (CNS) tumors.[1] More than 40% of patients experience at least one clinically evident seizure before surgery, increasing to over 60% in low-grade gliomas.[2] Seizures severely impact the quality of life for glioma patients and may affect surgical outcomes, particularly for those experiencing frequent

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preoperative seizures or refractory epilepsy. A high seizure burden, such as frequent seizures, can also lead to poor epilepsy prognosis.[3–6] The exact causes of seizures remain unclear, although multiple factors including tumor location, tumor pathology, and changes in the surrounding microenvironment have been shown to be associated with glioma associated epilepsy (GRE).[1,7–9] Given the complex nature of seizure triggers, relying on a single mechanism to explain and predict epilepsy may be inadequate.

Tumor location is an important factor in the occurrence of seizures in glioma patients.[10] However, the relationship between tumor location and seizure burden remains unclear. This is largely due to the fact that many observational studies classify tumor location according to traditional brain lobes, which diminishes statistical accuracy.[11] Specifically, for tumors affecting multiple brain lobes, nonrelevant areas might be incorrectly categorized as seizure-related regions, complicating the accurate identification of the responsible brain regions for seizure onset. Several studies have suggested that GRE may be associated with temporal lobe involvement, while others have indicated that frontal lobe involvement is more likely to lead to seizures. There is no clear consensus among these studies.[10,12,13] The discrepancies may be attributed to variations in tumor volume or differences in inclusion criteria.

Voxel-based lesion-symptom mapping (VLSM) is a lesion-symptom localization method based on imaging studies, initially applied to stroke patients.[14] This method allows for precise voxel-level symptom localization, improving accuracy compared to traditional approaches.[14] It effectively reduces statistical errors caused by tumors invading multiple brain lobes.[12] However, unlike in stroke patients, tumors can exert pressure on and damage normal brain tissue, potentially leading to functional compensation.[15] Moreover, seizures are associated with various factors beyond location.[8] Therefore, while VLSM may provide a more accurate localization of damage-related brain regions, it may not be comprehensive and should be considered alongside other clinical factors.

Thus, the aims of this retrospective study were: 1) to use quantitative VLSM analysis to identify brain regions most associated with the seizure burden in patients with diffuse gliomas; and 2) to determine whether the identified.

Methods

Patients and Clinical Factors

All data did not contain any personal identifying information. The study was conducted in accordance with the Declaration of Helsinki, the protocol was approved by the Ethics Committee of Beijing Tiantan Hospital and all patients provided written informed research consent.

This study retrospectively reviewed 1158 patients with diffuse gliomas treated at Beijing Tiantan Hospital from January 2020 to December 2023. Eligible patients included were those with primary diffuse gliomas, diagnosed based on postoperative pathological examination and aged ≥18 years. The exclusion criteria were: 1) Patients with insufficient information in their medical records to assess seizure status; 2) patients with missing or poor-quality preoperative MRI data that did not meet processing requirements; 3) patients without essential molecular pathology data (isocitrate dehydrogenase [IDH], 1p/19q, and Ki-67 index); and 4) patients who had received other anti-tumor treatments, such as biopsy, radiotherapy, or chemotherapy before admission. A total of 735 patients met the inclusion criteria and were enrolled in this study. The clinical and pathological characteristics of the included patients are detailed in Table 1.

Among the 735 patients, 357 had tumors located in the left hemisphere, while 378 had tumors in the right hemisphere. A total of 448 patients experienced preoperative seizures (217 in left), whereas 287 did not (140 in left). According to the latest 2021 CNS WHO classification, there were 372 cases of WHO grade 2 (low-grade glioma [LGG]) tumors and 363 cases of WHO grade 3 or 4 (high-grade glioma [HGG]) tumors.[16]

Clinical factors analyzed in the risk assessment included sex, age, tumor laterality, IDH gene mutation status, 1p/19q codeletion status, Ki-67 index, and tumor volume. Histopathological and molecular pathological evaluations were conducted on all patient specimens. The IDH mutation status was assessed via pyrosequencing, while 1p/19q codeletion status was determined through fluorescence in situ hybridization analysis. The Ki-67 index was assessed using immunohistochemistry and categorized based on the percentage of positive cells: "+" indicated a positive cell rate of less than 10%, "++" represented a positive cell rate between 10% and 50%, and "+++" denoted a rate exceeding 50%.

Epilepsy Assessment

The evaluation of patients' epilepsy history was primarily based on their medical records at admission. Patients were classified into the epilepsy group (Ep group) and the non-epilepsy group (nEp group) based on the presence of seizures within the 6 months prior to surgery. For the Ep group, patients had experienced at least one seizure, diagnosed by a professional clinician, within the 6 months before surgery. The seizure diagnosis was determined according to the ILAE 2017 classification criteria.[17] Furthermore, the number of seizures occurring within the 6 months before admission was recorded and categorized as 0, 1, 2, or at least 3. Seizure burden was defined as the number of clinical seizures experienced by the patient in the 6 months prior to surgery. The seizure burden was classified into three categories: none ($N = 0$), low burden ($N = 1$), and high burden ($N \geq 2$) according to the number of seizures. Seizures presenting as status epilepticus on the day of occurrence were counted as a single seizure.

Table 1. Demographic and Baseline Characteristics of Patient Cohort

Variables	Value ($N = 735$)
Sex (female/male), *N* (%)	312/423 (42.4/57.6)
Age (years), mean ± SD	43.44 ± 11.874
WHO 2021 grade, *N* (%)	
Grade 2	372 (50.6)
Grade 3	147 (20.0)
Grade 4	216 (29.4)
Pathology, *N* (%)	
Astrocytoma, IDH-mutant	245 (33.33)
Oligodendroglioma	264 (35.92)
Glioblastoma, IDH-wild	208 (28.30)
Astrocytoma, NOS	16 (2.18)
Oligodendroglioma, NOS	2 (0.27)
Side of tumors (left/right), *N* (%)	357/378 (48.6/51.4)
Preoperative epilepsy, *N* (%)	
Yes	448 (61.0)
No	287 (39.0)
Seizures burden in 6 months, *N* (%)	
0	294 (39.9)
1	208 (28.2)
2	65 (8.8)
≥3	168 (22.8)
Tumor volume (cm^3), median (IQR)	52.704 (24.299–97.066)
Tumor-involved brain regions, *N* (%)	
Frontal	566 (77.0)
Temporal	224 (30.5)
Insula	154 (21.0)
Parietal	125 (17.0)
Occipital	34 (4.6)
IDH 1/2 status, *N* (%)	
Wild	187 (25.4)
Mutant	548 (74.6)
1p/19q status, *N* (%)	
Noncodeletion	463 (63.0)
Codeletion	272 (37.0)
Ki-67 index, *N* (%)[a]	
+	383 (52.1)

Table 1. Continued

Variables	Value ($N = 735$)
++	295 (40.1)
+++	57 (7.8)

SD = standard deviation; IQR = interquartile range.
[a]+: Ki-67 (~10%); ++: Ki-67 (10%–50%), +++: Ki-67 (50%~).

MRI Acquisition and Preprocessing

All patients underwent MRI scans on a 3.0 T scanner at Beijing Tiantan hospital (Prisma, Siemens Healthcare, Erlangen, Germany or Discovery MR750, General Electric Healthcare, Waukesha, USA). T2-weighted images were used for tumor mask delineation and volume calculation. The T2 image parameters included: repetition time = 5020 msec; echo time = 105 msec; flip angle = 150.0°; field of view = 230 × 230 mm^2; voxel size = 0.51 × 0.51 × 5 mm^3; matrix size = 314 × 448 (Prisma, Siemens Healthcare) and repetition time = 7385.029 msec; echo time = 106.344 msec; flip angle = 142.0°; field of view = 240 × 240 mm^2; voxel size = 0.47 × 0.47 × 5.5 mm^3; matrix size = 384 × 384 (Discovery MR750, GE Medical System). For all patients, the tumor and adjacent abnormal high-signal areas in the T2-weighted images were considered as the involved regions. To account for mass effects and the impact of edema on brain tissue, both the tumor and the surrounding high-signal areas indicative of edema were included in the tumor mask.

The preprocessing of MRI data for VLSM involved several steps, including tumor segmentation, normalization of the tumor mask, and mask overlay. Firstly, tumor mask delineation was performed by two experienced neurosurgeons (T.L. and Q.L., >5 years of experiences in diagnosis) using 3D Slicer (https://www.slicer.org).[18] During the delineation process, the two neurosurgeons did not communicate with each other and were both blinded to the patients' clinical information. For the final tumor mask, the delineation by author T.L. served as the primary reference, with author Q.L.'s mask used for double-checking. If the overlap between the two authors' tumor masks was less than 5%, author T.L.'s mask was selected as the final mask for further analysis. If the overlap exceeded 5%, a senior neurosurgeon (L.W., >10 years' experience) made the final decision. The segmented tumor mask was then normalized to the ICBM 152 Nonlinear Atlases template using the ANTsPy toolbox (https://github.com/ANTsX/ANTsPy) within a Python 3.7 environment.[19] All voxel dimensions were standardized to 1 × 1 × 1 mm^3. The standardized tumor mask was visually inspected again by the senior neurosurgeon (L.W.) to verify the accuracy of segmentation and normalization. After standardization, the tumor volume was calculated and volume quartiles (Q1, Q2, and Q3) determined. To evaluate its impact on epilepsy, tumor volume was categorized as low (<Q1), moderate (Q1–Q3), or high (>Q3). The procedures for tumor segmentation and registration are illustrated in Figure 1.

VLSM Analysis

VLSM analysis was conducted using NiiStat software version 1.1 (available at https://github.com/neurolabusc/NiiStat) in MATLAB (R2020b). To account for tumor laterality, patients were divided into left-sided tumor and right-sided tumor groups, and overlap maps of all tumor-affected regions were created separately for each group. To minimize statistical errors due to small sample sizes, voxels with fewer than five overlapping tumors were excluded from the overlap map calculations. Seizure-related brain regions were analyzed separately for left-sided and right-sided groups.

Seizure-related brain regions were identified as voxels exhibiting statistically significant differences in the VLSM analysis. To minimize errors caused by tumor involvement only at the margins of relevant areas, the voxels with the most significant statistical differences (ie, those with the highest *z*-values) were identified as the peak voxel. Patients with tumors affecting the peak voxel were classified as "VLSM+" and those without involvement of the peak voxel were classified as "VLSM-."

Statistical Analysis

In VLSM analysis, a generalized linear model was used to evaluate the linear relationship between voxel locations on MRI and seizure frequency (0, 1, 2, ≥3), with statistical parameters computed for each voxel. All statistical tests in VLSM were one-tailed, and statistical significance was determined after 1000 permutations with a threshold of $P < 0.05$. Univariable and multivariable binary logistic regression analyses were then conducted to identify independent risk factors for preoperative GRE using the R project (version 4.4.0, available at www.r-project.org). To analyze risk factors associated with increased seizure frequency, patients were categorized into three groups based on seizure burden (none, low, and high), and both univariable and multivariable ordinal

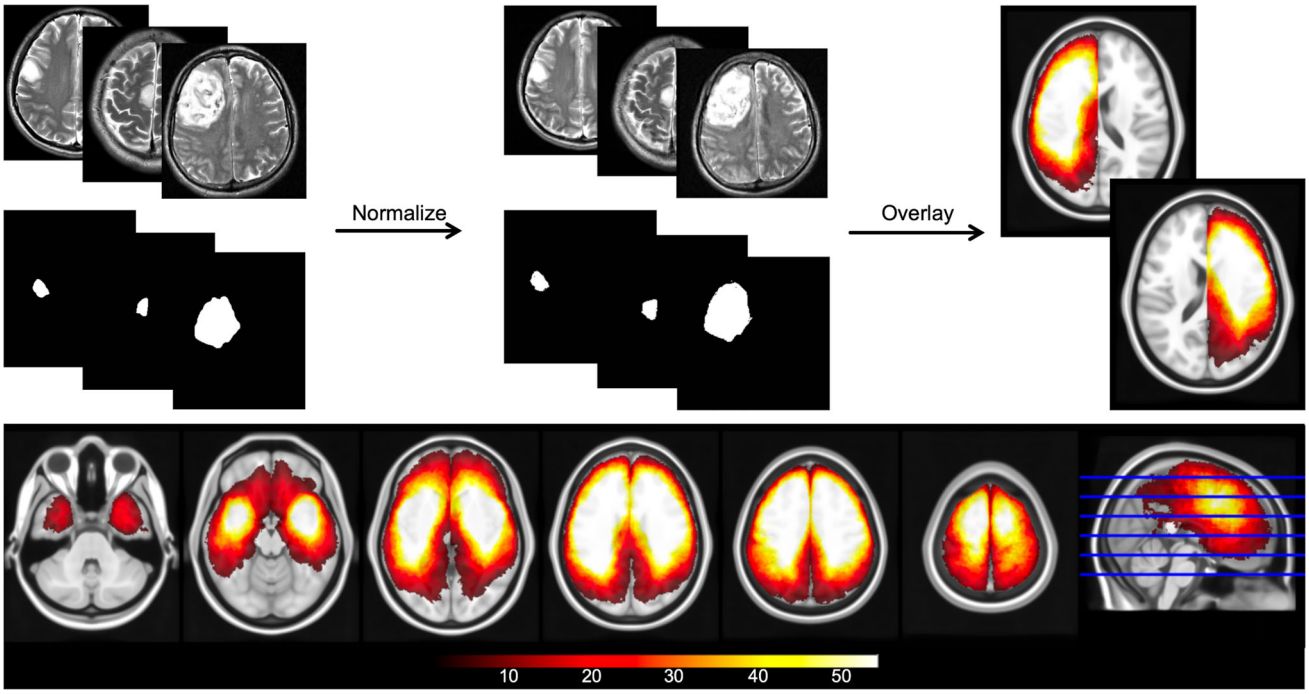

Figure 1: The workflow of tumor MRI image processing and tumor overlap mapping. Tumor masks from 735 patients were overlaid onto the standard brain template. Brighter colors indicate a higher number of overlapping patients in the corresponding region.

logistic regression analyses were performed using the "stats," "MASS," and "brant" packages. Variables with a *P*-value <0.2 in univariable analysis were included in the subsequent multivariable analysis. Parallelism tests and multicollinearity checks were performed on the included risk factors. A variance inflation factor less than 10 was considered indicative of no significant multicollinearity. The odds ratio (OR) and corresponding 95% confidence intervals (95% CI) were used to evaluate the impact of the included factors on the outcome measures. All statistical tests were two-tailed, and a *P*-value <0.05 was considered statistically significant.

In order to observe whether peak voxel involvement showed differences between low- and high-grade tumors, the probability of GRE was statistically assessed for both peak voxel-affected and nonaffected patients separately analyzed within low- and high-grade glioma groups, through the application of the chi-square test.

Results

VLSM Analysis Results

Significant overlap of tumor masks was observed in the bilateral frontal, temporal, insular, parietal, and occipital lobes. The extent of overlapping lesions is illustrated in Figure 1, with brighter colors on the color bar representing a higher number of overlapping patients.

In the VLSM analysis, significant correlations were identified between preoperative seizure burden and the bilateral temporal lobe, insular lobe, and portions of the frontal lobe. The peak voxels were located in the right hippocampus and the left insular cortex, exhibiting the most statistically significant differences related to preoperative seizure burden (z_{left} = [52, 148, 66], z_{right} = [118, 134, 53], Figure 2a and b), particularly in the head of the right hippocampus. After grouping the tumors into high- and low-grade gliomas, the results showed that irrespective of tumor grade, the peak voxel involvement was significantly associated with preoperative seizure (Table 2).

Multivariable Logistic Regression Between Epilepsy and Clinical Factors

Compared to nonepileptic patients, no significant differences were observed in sex ($P = 0.573$) and IDH mutation status ($P = 0.315$) after binary multivariate logistic regression analysis. Age (OR = 0.97), 1p/19q codeletion (OR = 1.51), moderate tumor volume (interquartile range, 24.229–97.066 cm^3), and involvement of the peak voxel (OR = 6.06) were significantly associated with preoperative seizures and were identified as independent risk factors for preoperative seizure occurrence (Table 3 and Figure 3a).

Multivariable Ordinal Logistic Regression Analysis of the Correlation Between Seizure Burden and Clinical Factors

The analysis showed that involvement of the peak voxel (OR = 6.98) was an independent risk factor for increased preoperative seizure burden (Table 4). Conversely, larger tumor volume (>97.066 cm^3) (OR = 0.49) and increasing age (OR = 0.98) were associated with a gradual decreasing in preoperative seizure burden (Figure 3b).

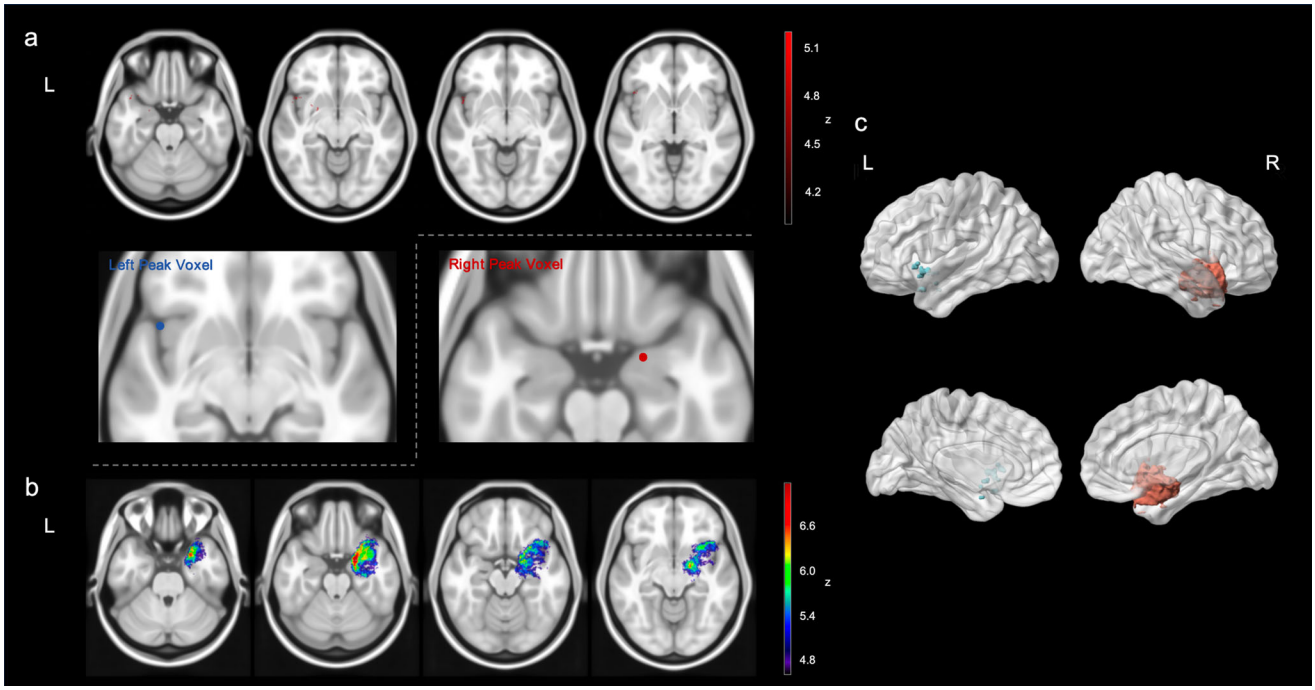

Figure 2: VLSM analysis showing seizure related brain regions. (a) When the tumor was located in the left hemisphere, epilepsy-related regions were found in the left insular cortex. (b) When the tumor was located in the right hemisphere, significant associations were observed between seizure burden and the medial temporal lobe, inferior frontal gyrus, and insular cortex. The color bar indicates the *z*-values from dark blue to red (least to most significant). Only significant voxels are shown (determined after 1000 permutations with a threshold of $P < 0.05$). (c) The illustration of the spatial locations of voxels with significant differences in the 3D brain.

Table 2. Differences in the Peak Voxel Between Low- and High-Grade Glioma (LGG and HGG) Groups

Seizures Burden in 6 Months Before Surgery	VLSM+	VLSM−	*P**
LGG			
0	3	126	<0.0001
1	5	114	
2	4	32	
≥3	31	57	
HGG			
0	7	158	0.0087
1	12	77	
2	2	27	
≥3	16	64	

*Result of chi-square test, calculated in SPSS version 27.

Discussion

Epilepsy is a common preoperative clinical symptom in glioma patients.[2] Frequent preoperative seizures severely affect patients' quality of life and impact postoperative epilepsy prognosis. For patients at high risk of seizures, early and proactive antiepileptic treatment may be beneficial in reducing the impact of epilepsy and preventing postoperative seizures after tumor resection.[2,13] In this study, VLSM analysis was

Table 3. Univariable and Multivariable Analyses of Risk Factors Associated With Preoperative Glioma-Related Epilepsy

	Univariable		Multivariable	
Variables	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**
Sex				
Female		1.00 (reference)		1.00 (reference)
Male	0.063	1.33 (0.98–1.79)	0.573	1.10 (0.80 – 1.51)
Age	<0.001	0.97 (0.95 – 0.98)	<0.001	0.97 (0.95 – 0.98)
Side of tumors				
Left		1.00 (reference)		
Right	0.928	1.01 (0.75–1.36)		
IDH status				
Wild		1.00 (reference)		1.00 (reference)
Mutant	0.038	1.43 (1.02 – 2.00)	0.315	0.80 (0.52 – 1.23)
1p/19q status				
Non-codeletion		1.00 (reference)		1.00 (reference)
Codeletion	0.026	1.42 (1.04 – 1.94)	0.028	1.51 (1.05 – 2.19)
Ki-67 index				
+		1.00 (reference)		
++	0.584	0.92 (0.67 – 1.25)		
+++	0.248	0.72 (0.41 – 1.26)		
Tumor volume (quartile)				
Q1		1.00 (reference)		1.00 (reference)
Q2	0.024	1.63 (1.07 – 2.50)	0.024	1.66 (1.07 – 2.57)
Q3	0.013	1.72 (1.12 – 2.64)	0.022	1.69 (1.08 – 2.65)
Q4	0.106	0.71 (0.47 – 1.07)	0.052	0.64 (0.40 – 1.00)
Peak voxel				
VLSM (−)		1.00 (reference)		1.00 (reference)
VLSM (+)	<0.001	5.13 (2.60 – 10.13)	<0.001	6.06 (2.96 – 12.43)

Q1: 0–24.229 cm^3; Q2: 24.229–52.704 cm^3; Q3: 52.704–97.066 cm^3, Q4: >97.066 cm^3.
OR = odds ratio; CI = confidence interval.

used to identify the brain regions associated with preoperative seizure burden and multivariable binary and ordinal logistic regression analyses were conducted to find the risk factors related to preoperative seizure burden. The findings indicate that tumor location is significantly associated with GRE, regardless of tumor grade and side. Specifically, involvement of the insula and the head of the hippocampus is associated with an increased risk of seizures in glioma patients. Furthermore, the multivariable binary logistic regression analysis showed that younger age, tumor involvement in peak voxel, moderate-sized tumor, and 1p/19q codeletion are independent risk factors for the occurrence of seizures, while involvement of the peak voxel is also an independent risk factor for increased seizure burden.

VLSM-based localization analysis allows for more precise identification of seizure-related brain regions. By performing statistical analysis at the voxel level, this method accurately pinpoints relevant voxels, avoiding the rough

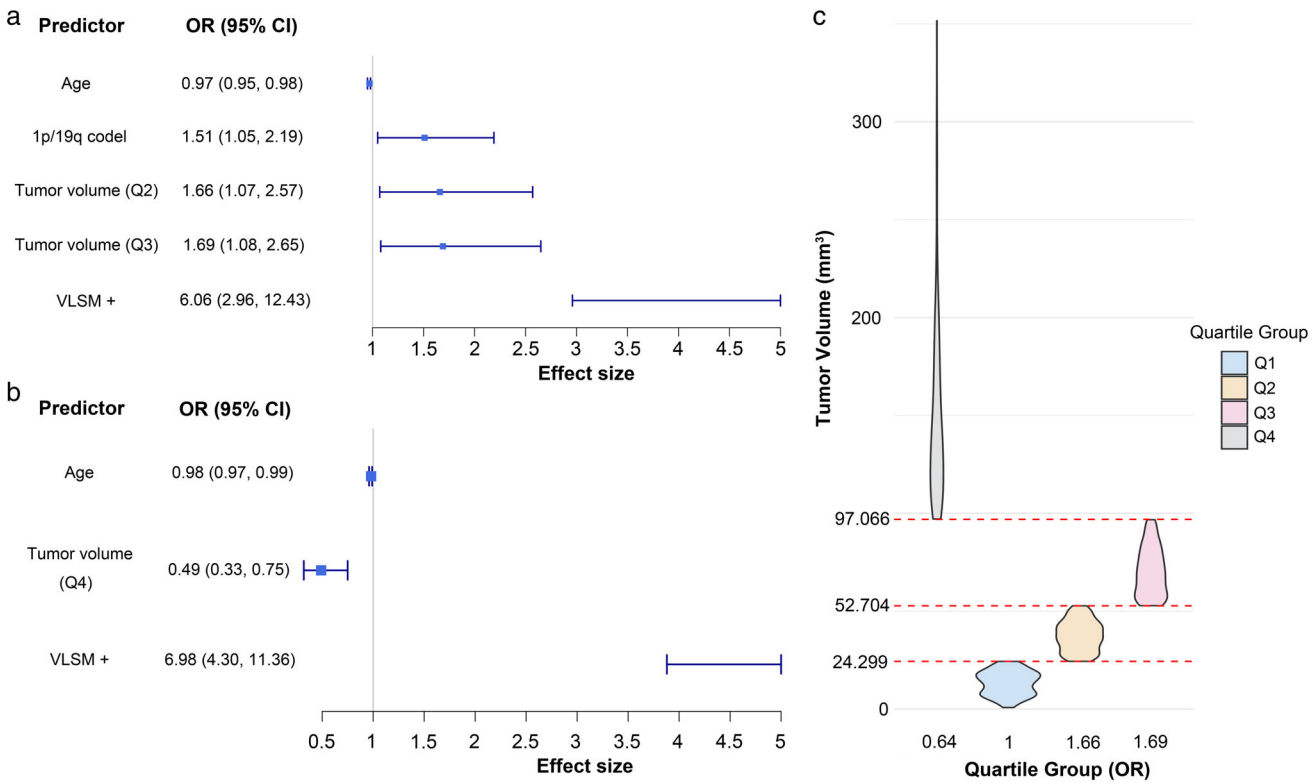

Figure 3: (a) Forest plot of odds ratio between preoperative seizure and non-seizure groups. (b) Forest plot of odds ratio for preoperative seizure burden. (c) Violin plot showing the distribution of tumor volume and odds ratio ranking based on (a). CI = confidence interval; OR = odds ratio.

estimation of tumor location. In the current study, voxels with significant differences were primarily located in the medial temporal lobe, the insula, and the inferior frontal gyrus, providing a more detailed localization of the seizure-related brain regions. Temporal lobe epilepsy, particularly mesial temporal lobe epilepsy, is one of the most common types of epilepsy in adults.[20] Studies have also shown a close association between the hippocampal region and the occurrence of refractory epilepsy.[21,22] The insula, due to its close anatomical association with the temporal lobe, is often affected by tumors in the temporal lobe.[23,24] Additionally, the insula occupies a unique position with complex functional subregions. Although the total cortical area occupied by the insula is relatively small, it has extensive fiber connections with other brain regions, particularly the frontal lobe, temporal lobe, amygdala, and subcortical structures.[25] This highlights the integrative and pivotal role of the insula in information transmission, which also explains why seizures originating from the insula are often complex and frequently refractory.[26,27]

In comparison with a previous study, Wang et al found that seizure-related brain regions in low-grade gliomas were located in the supplementary motor area of the frontal lobe, as well as in parts of the temporal lobe and insula, particularly in patients with simple partial seizures and complex partial seizures.[12] These findings show some overlap with the positive regions identified in the current study. In addition, although the current study did not categorize seizure-related areas based on seizure types, involvement of these regions was shown to increase the risk of seizures by analyzing seizure frequency. It also included patients with gliomas of all grades. While some studies have suggested differences in seizure incidence between glioma grades, the current study found that the peak voxels showed significant differences in seizure burden in both low- and high-grade gliomas.[2,28] This indicates that the role of this location in seizures is less influenced by tumor grade and may represent a common risk area across all glioma grades.

In this study, in addition to tumor location, multivariable binary logistic regression found that three clinical factors (age, 1p/19q codeletion, and tumor volume) were associated with preoperative seizures. Previous studies have confirmed that younger patients are more prone to seizures.[1,29,30] Furthermore, patients with 1p/19q codeletion, when accompanied by IDH mutations, are classified as oligodendrogliomas in integrated diagnostics, which are typically slow-growing tumors and have a higher risk of seizure occurrence compared to astrocytoma.[28] A previous study based on brain networks has suggested that epilepsy is a network disease, with seizures associated with changes and remodeling of brain networks.[31] Slow tumor growth is more likely to lead to brain network reorganization rather than destruction, thereby increasing the

Table 4. Univariable and Multivariable Ordinal Analysis of Seizure Burden Before Surgery

	Univariable		Multivariable	
Variables	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**
Sex				
Female		1.00 (reference)		1.00 (reference)
Male	0.088	1.27 (0.97–1.66)	0.939	1.01 (0.76 – 1.34)
Age	<0.001	0.97 (0.96 – 0.98)	<0.001	0.98 (0.96 – 0.99)
Side of tumors				
Left		1.00 (reference)		
Right	0.841	0.97 (0.75 – 1.27)		
IDH status				
Wild		1.00 (reference)		
Mutant	0.562	1.10 (0.80 – 1.50)		
1p/19q status				
Non-codeletion		1.00 (reference)		
Codeletion	0.228	1.18 (0.90 – 1.56)		
Ki-67 index				
+		1.00 (reference)		
++	0.813	1.03 (0.78 – 1.37)		
+++	0.612	0.87 (0.52 – 1.47)		
Tumor volume (quartile)				
Q1		1.00 (reference)		1.00 (reference)
Q2	0.033	1.51 (1.03–2.21)	0.068	1.43 (0.97–2.11)
Q3	0.028	1.53 (1.05–2.23)	0.129	1.36 (0.92–2.01)
Q4	0.031	0.65 (0.44–0.96)	<0.001	0.49 (0.32–0.75)
Peak voxel				
VLSM (−)		1.00 (reference)		1.00 (reference)
VLSM (+)	<0.001	5.21 (3.22–8.43)	<0.001	6.47 (3.88–10.80)

Q1: 0–24.229 cm^3; Q2: 24.229–52.704 cm^3; Q3: 52.704–97.066 cm^3; Q4: >97.066 cm^3.
OR = odds ratio; CI = confidence interval.

risk of seizures.[32] Chang et al also found that oligodendrogliomas are more likely to cause seizures.[7] However, the role of 1p/19q in seizure occurrence remains somewhat controversial, as many genes are affected by chromosomal deletions, and the underlying mechanisms of seizures related to 1p/19q codeletion require further investigation.[33,34]

Tumor volume has also been reported to be an important risk factor for GRE. Previous findings are consistent with the conclusions of the current study. Yu et al found that in high-grade gliomas, the risk of seizures increased when tumor volume was ≤60 cm^3, although no significant difference was observed after multivariable regression.[13] Skardelly et al identified tumor volume <64 cm^3 as an independent predictor of seizures.[29] Moreover, Bech et al found that a tumor diameter <40 mm was significantly associated with seizures; however, due to the irregular shape of tumors and the lack of calculation of tumor volume, analysis based on tumor volume may provide a more accurate assessment than analyses based on diameter.[8] Several current studies use binary classification for

tumor volume but lack a precise volume threshold standard and overlook the possibility that smaller tumors may not yet be sufficiently epileptogenic.[13,29] In the current study, quartile-based classification of tumor volume was used, which provides a more detailed categorization and avoids interference from very small or very large tumor volumes. Notably, we found that the risk of seizures was significantly increased in the Q2 and Q3 quartiles compared to the Q1 quartile. However, the risk of seizures in the Q4 quartile was not significantly different from that in the Q1 quartile. This suggests that tumors with either very small or very large volumes are less likely to cause seizures compared to tumors with moderate volume. The results of the current study contribute to a more detailed understanding of the relationship between tumor volume and seizure occurrence. Combining these findings with the results from peak voxel analysis and previous brain network studies, it appears that very small tumors may not impact the peak voxel region or produce significant effects on surrounding cortex. Conversely, very large tumors often involve neurological impairment and disruption of brain networks, which may interfere with seizure onset and propagation, thereby reducing the risk of seizures.[35]

Increased burden of preoperative seizures may lead to poor postoperative seizure outcomes and even evolve into refractory epilepsy.[4] This may be related to adaptive changes in brain networks or brain structure, such as alterations in brain network topology or gray matter atrophy.[4,5,32,36,37] In the current study, ordinal logistic regression showed that when tumors involved the VLSM+ regions, patients experienced multiple seizures preoperatively, whereas larger tumor volume and age showed a negative correlation with preoperative seizures burden. This indicates that tumor location plays an important role in the occurrence and development of epilepsy compared to other factors. Similar to primary epilepsy, the hippocampus plays a significant hub role in the occurrence and propagation of seizures.[21,22] Patients with hippocampal involvement are more likely to experience frequent seizures. In primary epilepsy, hippocampal sclerosis is one of the major causes of epilepsy.[21] This may be due to synaptic plasticity in the hippocampal region and increased sensitivity to glutamate, leading to abnormal hyper-synchronous discharges in remaining hippocampal neurons.[38,39] For GRE, changes in the microenvironment such as alterations in glutamate, γ-aminobutyric acid, and ion channel dysfunction have been shown to play an important role in seizure activity.[9,40] This may be a potential reason for the increased seizure burden when gliomas involve the hippocampus. However, further studies are needed to explore the effects of gliomas on the hippocampus.

Limitations

Firstly, considering the WHO 2021 CNS tumor classification, more molecular pathological markers should be considered as clinical factors. However, only a subset of patients underwent comprehensive molecular pathology testing, which would have reduced the sample size. Additionally, due to the lack of postoperative data for some patients, such as the extent of tumor resection and postoperative medication, this study did not analyze seizure prognosis. Although previous studies have shown that factors like seizure burden are associated with poor seizure prognosis, it remains unclear whether the peak voxels and seizure burden in the current dataset are related to seizure prognosis.[3–5] Further studies with larger sample sizes, comprehensive seizure prognosis data and an independent test set are needed for more precise analysis and external validation of our findings.

Conclusion

This study found that tumor volume, peak voxel, and 1p/19q codeletion are independent risk factors for preoperative seizures in glioma patients, with involvement of the peak voxel region being associated with a higher seizure burden.

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Author Contributions

Tianshi Li: study concept and design, data acquisition and analysis, formal analysis and investigation, writing—original draft preparation. Lei Wang: study concept and design, funding acquisition, supervision. Qiuling Li: data acquisition and analysis, writing—original draft preparation, writing—review and editing. Gan You: formal analysis and investigation, supervision. Xing Fan: funding acquisition. All authors contributed to the article and approved the submitted version. The authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

References

1. Li L, Fang S, Li G, et al. Glioma-related epilepsy in patients with diffuse high-grade glioma after the 2016 WHO update: Seizure characteristics, risk factors, and clinical outcomes. J Neurosurg 2022;136(1):67-75.
2. Liang S, Fan X, Zhao M, et al. Clinical practice guidelines for the diagnosis and treatment of adult diffuse glioma-related epilepsy. Cancer Med 2019;8(10):4527-4535.
3. Sillanpää M, Schmidt D. Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. Brain 2009; 132(Pt 4):989-998.
4. Ius T, Pauletto G, Isola M, et al. Surgery for insular low-grade glioma: Predictors of postoperative seizure outcome. J Neurosurg 2014;120(1): 12-23.
5. Tan ZR, Long XY, Yang ZQ, et al. Younger age at surgery and lesser seizure frequency as prognostic factors for favorable seizure-related

outcome after glioma resection in adults. Oncotarget 2017;8(55): 93444-93449.

6. Alharbi HM, Pinchefsky EF, Tran MA, et al. Seizure burden and neurologic outcomes after neonatal encephalopathy. Neurology 2023; 100(19):e1976-e1984.
7. Chang EF, Potts MB, Keles GE, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg 2008;108(2):227-235.
8. Bech KT, Seyedi JF, Schulz M, Poulsen FR, Pedersen CB. The risk of developing seizures before and after primary brain surgery of low- and high-grade gliomas. Clin Neurol Neurosurg 2018;169:185-191.
9. Buckingham SC, Robel S. Glutamate and tumor-associated epilepsy: Glial cell dysfunction in the peritumoral environment. Neurochem Int 2013;63(7):696-701.
10. Zhang J, Yao L, Peng S, Fang Y, Tang R, Liu J. Correlation between glioma location and preoperative seizures: A systematic review and meta-analysis. Neurosurg Rev 2019;42(3):603-618.
11. Lynam LM, Lyons MK, Drazkowski JF, et al. Frequency of seizures in patients with newly diagnosed brain tumors: A retrospective review. Clin Neurol Neurosurg 2007;109(7):634-638.
12. Wang Y, Qian T, You G, et al. Localizing seizure-susceptible brain regions associated with low-grade gliomas using voxel-based lesion-symptom mapping. Neuro Oncol 2015;17(2):282-288.
13. Yu Z, Zhang N, Hameed NUF, et al. The analysis of risk factors and survival outcome for Chinese patients with epilepsy with high-grade glioma. World Neurosurg 2019;125:e947-e957.
14. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion-symptom mapping. Nat Neurosci 2003;6(5):448-450.
15. Fang S, Li L, Weng S, et al. Contralesional sensorimotor network participates in motor functional compensation in glioma patients. Front Oncol 2022;12:882313.
16. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro Oncol 2021; 23(8):1231-1251.
17. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):522-530.
18. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the quantitative imaging network. Magn Reson Imaging 2012;30(9):1323-1341.
19. Fonov VS, Evans AC, McKinstry RC, Almli CR, Collins DL. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. Neuroimage 2009;47:S102.
20. Pascual MR. Temporal lobe epilepsy: Clinical semiology and neurophysiological studies. Semin Ultrasound CT MR 2007;28(6):416-423.
21. Thom M. Review: Hippocampal sclerosis in epilepsy: A neuropathology review. Neuropathol Appl Neurobiol 2014;40(5):520-543.
22. Chan S, Bello JA, Shinnar S, et al. Hippocampal malrotation is associated with prolonged febrile seizures: Results of the FEBSTAT study. AJR Am J Roentgenol 2015;205(5):1068-1074.
23. Tatum WO 4th. Mesial temporal lobe epilepsy. J Clin Neurophysiol 2012;29(5):356-365.
24. Feys O, Goldman S, Lolli V, et al. Diagnostic and therapeutic approaches in refractory insular epilepsy. Epilepsia 2023;64(6):1409-1423.
25. Almashaikhi T, Rheims S, Jung J, et al. Functional connectivity of insular efferences. Hum Brain Mapp 2014;35(10):5279-5294.
26. Solanki C, Williams J, Andrews C, Fayed I, Wu C. Insula in epilepsy—"untying the gordian knot": A systematic review. Seizure 2023;106: 148-161.
27. Blauwblomme T, David O, Minotti L, et al. Prognostic value of insular lobe involvement in temporal lobe epilepsy: A stereoelectroencephalographic study. Epilepsia 2013;54(9):1658-1667.
28. Avila EK, Tobochnik S, Inati SK, et al. Brain tumor-related epilepsy management: A Society for Neuro-oncology (SNO) consensus review on current management. Neuro Oncol 2023;26:7-24.
29. Skardelly M, Brendle E, Noell S, et al. Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: A retrospective observational single center study. Ann Neurol 2015;78(6):917-928.
30. You G, Sha ZY, Yan W, et al. Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: A clinicopathological study. Neuro Oncol 2012;14(2):230-241.
31. Fang S, Zhou C, Fan X, Jiang T, Wang Y. Epilepsy-related brain network alterations in patients with temporal lobe glioma in the left hemisphere. Front Neurol 2020;11:684.
32. Royer J, Bernhardt BC, Lariviere S, et al. Epilepsy and brain network hubs. Epilepsia 2022;63(3):537-550.
33. Shen S, Bai Y, Zhang B, Liu T, Yu X, Feng S. Correlation of preoperative seizures with a wide range of tumor molecular markers in gliomas: An analysis of 442 glioma patients from China. Epilepsy Res 2020;166: 106430.
34. Huang L, You G, Jiang T, Li G, Li S, Wang Z. Correlation between tumor-related seizures and molecular genetic profile in 103 Chinese patients with low-grade gliomas: A preliminary study. J Neurol Sci 2011;302(1–2):63-67.
35. Zhou C, Fang S, Yang J, Wang Y, Wang L. Epilepsy-related white matter network changes in patients with frontal lobe glioma. J Neuroradiol 2023;50(2):258-265.
36. Bonilha L, Rorden C, Appenzeller S, Coan AC, Cendes F, Li LM. Gray matter atrophy associated with duration of temporal lobe epilepsy. Neuroimage 2006;32(3):1070-1079.
37. Norden AD, Blumenfeld H. The role of subcortical structures in human epilepsy. Epilepsy Behav 2002;3(3):219-231.
38. Koyama R, Tao K, Sasaki T, et al. GABAergic excitation after febrile seizures induces ectopic granule cells and adult epilepsy. Nat Med 2012; 18(8):1271-1278.
39. Kasperaviciute D, Catarino CB, Matarin M, et al. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. Brain 2013;136(Pt 10):3140-3150.
40. Lange F, Hörnschemeyer MF, Kirschstein T. Glutamatergic mechanisms in glioblastoma and tumor-associated epilepsy. Cells 2021;10(5):1226.