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Clinical study

Analysis of the short-term outcomes and risk factors of seizure relapse in patients with gliomas after antiepileptic drugs withdrawal

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Objective: The optimal timing for glioma patients to stop taking antiepileptic drugs (AEDs) and the risk factors of seizure relapse have not been determined. Here, we explored the short-term outcomes and risk factors of seizure relapse in glioma patients after withdrawal of AEDs.

Methods: 91 patients with gliomas who had no seizures at least 2 years after surgery were enrolled in the study. The patients were followed up for 1 year or until the relapse of seizure after AEDs withdrawal. The risk factors of seizure relapse were analyzed by univariate and multivariate analysis. The optimal discrimination point was determined by plotting a receiver operating characteristic (ROC) curve to explore the relationship between the number of risk factors and seizure relapse.

Results: 28 patients (30.8%) relapsed during the follow-up period while 63 patients (69.2%) remained seizure-free. Of the 28 relapsed patients, 20 (71.4%) relapsed within the first 6 months after the AEDs withdrawal. Multivariate analyses revealed that subtotal resection ($p = 0.026$), IDH1 mutation ($p = 0.019$), and combined use of AEDs ($p = 0.037$) were independent risk factors for seizure relapse in glioma patients. ROC curve based on the seizure relapse showed that the sensitivity was 0.821 and 1–specificity was 0.238, corresponding to 1.5 independent risk factors for each patient.

Conclusion: To obtain a favorable outcome for glioma patients with preoperative seizures, only patients with less than two independent risk factors for seizure relapse should consider discontinuing AEDs.

1. Introduction

Epilepsy is probably earliest and only clinical manifestation of gliomas, with a incidence rate of 40% to 90% [1]. If not controlled, epileptic seizures could have adverse effect on health-related quality of life (QOL) and pose a risk of morbidity. In addition to epileptic seizures, the glioma itself and the antitumor therapy may lead to behavioral changes, cognitive dysfunction, and a decline in QOL. However, up to 15–50% of glioma patients are unable to get rid of epilepsy in clinical practice, despite postoperative adjuvant therapy such as antiepileptic drugs (AEDs) [2]. There is no doubt that glioma patients with epileptic seizures need AEDs treatment. On the other hand, these drugs are associated with an increasing number of intangible adverse effects, such as long-term treatment, pill burden, cognitive and behavioral changes, and social stigma [3]. Although there is no reliable evidence to guide the the withdrawal time of AEDs in glioma patients without seizures, some scholars consider that the waiting period of at least 2 years is the best [4]. The recurrence rates of seizures in most patients with intra-axial brain tumors was as high as 27% after withdrawal of AEDs [5]. At present, there are controversies on the withdrawal of AEDs in patients with gliomas, comparing the risk of seizure relapse and the burden of AEDs.

Patients with gliomas who have received AEDs and have been seizure-free for an extended period should consider discontinuing AEDs, especially those with severe side effects. Nevertheless, the risk of seizure relapse follows. Therefore, the potential benefits and hazards of drug withdrawal should be evaluated. And it is of great significance to explore the related risk factors of seizure recurrence in glioma patients after AEDs withdrawal. In fact, 22 factors have been reported to be associated with seizure recurrence in different populations through different research methods, including the age at onset of epilepsy, history of febrile seizures, and the number of seizures before remission [4]. However, most of these studies are not aimed at glioma patients. In addition, the relationship between the number of risk factors per patient and the likelihood of seizure relapse has not been explored. Here, we designed a retrospective study involving 91 patients in a single institution to explore the short-term outcomes and risk factors

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for seizure relapse in seizure-free patients with gliomas after withdrawal of AEDs. Finally, we propose clinical practice guideline for glioma patients to discontinue AEDs.

2. Patients and methods

2.1. Patients

This retrospective study included 103 patients with glioma who underwent surgery at the Department of Neurosurgery in Renmin Hospital of Wuhan University from September 1, 2015 to December 30, 2019. The inclusion criteria were as follows: 1) New diagnosis of non-glioblastoma (WHO grade I-III) according to the 2016 WHO classification, patients with glioblastoma were not included due to the short overall-survival time; 2) a preoperative electroencephalogram (EEG) confirmed the diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) standard published in 2010, while the cortical EEG localization showed that the tumor site was roughly the same as the epileptic foci; 3) The patient received one or more AEDs after the operation and had no seizures within 2 years before attempting to discontinue the adjuvant therapy; 4) The isocitrate dehydrogenase 1 (IDH1) mutational status, 1p/19q codeletion status, and MGMT promoter methylation status were detected by IHC, FISH and digital qPCR; 5) Postoperative adjuvant radiotherapy and chemotherapy were performed as needed, and the relevant details were recorded. The criteria for exclusion were as follows: 1) History of epilepsy caused by family heredity, craniocerebral trauma, brain dysplasia, cerebrovascular disease or intracranial infection; 2) Pediatric patients were excluded from all gliomas; 3) The patient lost follow-up or died of other causes; 4) History of neuropsychiatric disorders. 12 out of 103 patients were excluded, 5 patients were followed up less than 1 year after the withdrawal of AEDs, 4 patients had no complete medical records, 3 patients suffered epilepsy relapse due to a sudden cessation of AEDs and 2 patients relapsed due to excessive alcohol consumption and lack of proper rest. The remaining 91 patients were enrolled in the study to assess the short-term outcome and to explore risk factors of seizure relapse associated with AED withdrawal.

Whether or not to discontinue the AEDs depended on the patient's own choice and situation. The pros and cons of drug withdrawal were discussed with the caregiver and/or patients themselves. The AEDs was reduced by 1/4 every 3 months for most of the patients who agreed to discontinue the AED, while 3 patients who failed to comply with these withdrawal requirements relapsed. During the discontinuation of AEDs, detailed information related to drug regimens and relapse was recorded every 3 months.

2.2. Definitions

The clinical and demographic characteristics of the patients were recorded and analyzed. Pre-and postoperative MRI was used to evaluate the clinical features of gliomas. All clinical characteristics mentioned above were assessed by independent follow-up. The classification of seizure types was defined according to the International League Against Epilepsy (ILAE) [6]. For the number of AEDs used to control epilepsy in each patient, monotherapy referred to patients taking a single drug, while the combination group referred to patients receiving two or more AEDs at the same time. Surgical removal of the gliomas was performed by senior neurosurgeons in all patients. All enrolled patients were tested for IDH1 status, the 1p/19q codeletion, and MGMT promoter methylation by molecular pathology. Gross total resection was defined as complete resection of the tumor with no residual tumor. Subtotal resection was defined as resection of a gross tumor by $\geq$ 90% [7]. The extent of resection was more than 50% in all selected patients. The adjuvant therapy after glioma surgery included radiotherapy and chemotherapy. Radiotherapy was done with conventional fractions dose of 1.8–2 Gy, 5 times a week, and the radiation doses was 54–60 Gy. The chemotherapy regimens for diffuse astrocytoma were nimustine hydrochloride (ACNU) before 2006 and temozolomide after 2006, while PAV [ACNU + vincristine (VCR) + procarbazine (PCZ)] for oligodendroglioma before 2006 and temozolomide after 2006. The enrolled patients were divided into relapsed (RE) group and the seizure-free (SF) group. The SF group included patients who did not relapse with epilepsy during the tapering period. The relapsed group included patients who relapsed within 1 year atfer the start of AEDs withdrawal.

2.3. Statistical analysis

The data was analyzed by SPSS Software version 23.0 and GraphPad Prism 7.0. A P value < 0.05 was considered statistically significant. Chi-square test and student's *t*-test were performed for categorical variables and continuous variables, respectively. Variables that were significantly different on univariate analysis were used as independent variable for multivariate analyses by the Cox proportional hazards model. To identify the association between the number of risk factors per patient and the relapse related to the withdrawal of AEDs, continuous variables were stratified, and the cutoff values were determined based on the Youden index in an ROC analysis.

3. Results

3.1. Demographic characteristics

A total of 91 patients (44 females and 47 males) met the inclusion criteria and were followed up. The follow-up time was 1 year or until seizure relapse after AED withdrawal, and the median follow-up time was 7.7 months. The age ranged from 17.9 to 53.6 years old and the mean age at seizure onset was 41.65 ± 8.97 years old. Both one type of seizure (44/91, 48.4%) and multiple types of seizure (47/91, 51.6%) occurred. For the patient's tumor site, 44 cases were located in the frontal or temporal lobe, and 47 cases in occipital or parietal lobe. 52 patients (52/91, 57.1%) had gross total resection of gliomas, and postoperative pathology confirmed that the gliomas were of WHO I-III (Fig. 1). In molecular pathology, IDH1 mutation was found in 42 cases (46.2%), 1p/19q codeletion was found in 45 cases (49.5%), and 33 cases (36.3%) displayed MGMT promoter methylation. For the postoperative adjuvant treatments, all patients received AEDs. Specifically, 52 patients (57.1%) received a single AED and 39 patients (42.9%) received multiple AEDs. In addition, 60 cases (65.9%) received chemotherapy, and 67 cases (73.7%) received radiotherapy. Among these patients, EEGs were recorded in 54 cases before AEDs withdrawal, of which 19 (19/54, 35.2%) had abnormal electrical activity. Among the 91 patients, 28 patients had tumor recurrence (Table 1).

3.2. Rate and time of seizure relapse within 1 year following the withdrawal of AEDs

28 cases (30.8%) relapsed within 1 year after the first withdrawal of AEDs, of which 20 (20/28, 71.4%) relapsed in the first 6 months and 8 (8/28, 28.6%) relapsed in the following 6 months. 63 (69.2%) of the 91 patients had not relapsed at the end of follow-up. The seizure relapses mostly occurred in the first 6 months after drug. withdrawal, and there was significant difference in the recurrence time of seizure within 1 year after AEDs withdrawal (Table 2).

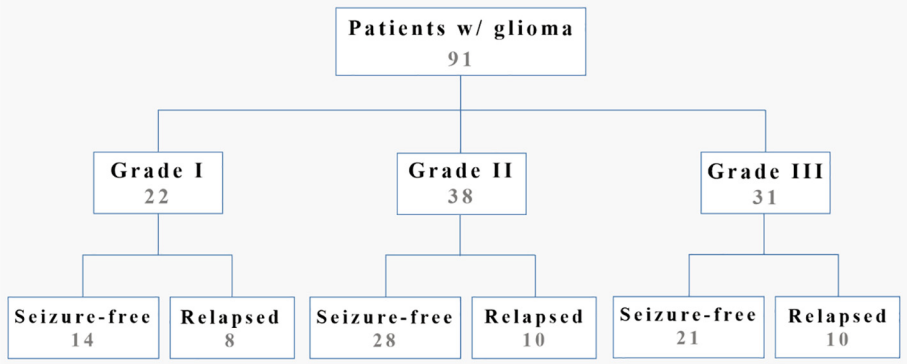

Fig. 1. Seizure outcome flow chart.

Table 1
Demographics and clinical characteristics of patients.

Variables	Seizure-free (n = 63)	Relapsed (n = 28)	p value
Age at onset			0.942
≥30 years	40	18	
>30 years	23	10	
Gender			0.807
Male	32	15	
Female	31	13	
Number of seizure type			0.002
Single type	40	4	
Multiple types	23	24	
Tumor location			0.031
Frontal	15	13	
Occipital	28	5	
Parietal	11	3	
Temporal	9	7	
Extent of resection			0.001
Gross-total resection	43	9	
Subtotal resection	20	19	
Grade of tumor			0.701
WHOI	14	8	
WHOII	28	10	
WHOIII	21	10	
IDH1 mutation			0.001
Yes	22	20	
No	41	8	
1p/19q codeletion			0.944
Yes	31	14	
No	32	14	
MGMT promoter methylation			0.942
Yes	23	10	
No	40	18	
Combination of AEDs			0.001
Single drug	43	9	
Combination	20	19	
Chemotherapy			0.804
Yes	48	22	
No	15	6	
Radiotherapy			0.751
Yes	47	20	
No	16	8	
Tumor recurrence			0.850
Yes	19	9	
No	44	19	
EEG results before withdrawal			0.984
Normal	24	11	
Abnormal	13	6	
Unknown	26	11	

3.3. Risk factors of relapse associated with AEDs withdrawal

Univariate analysis showed that patients with frontotemporal lobe lesions were more likely to relapse than patients with other parts of the brain (p = 0.003). Patients with STR of glioma showed a greater tendency to relapse than those with GTR (p = 0.001). And compared with wild type IDH1, IDH1 mutation patients were more likely to relapse (p = 0.001). What's more, patients with multiple types of seizures were more likely to relapse than patients who experienced a single type of seizure (p = 0.002). At last, patients treated with combined AEDs to control seizures were more likely to relapse than those taking a single drug (p = 0.001).

There was no statistically significant difference in the following variables between the SF and RE groups: gender, age at onset of seizure, tumor grade, family history of seizure, molecular pathology result of 1p/19q codeletion and MGMT promoter methylation, postoperative adjuvant treatment of radiotherapy, chemotherapy of temozolomide, tumor recurrence, and EEG results before withdrawal (Table 1).

The results of multivariate analyses using Cox proportional hazard model are shown in Table 3. Three factors were identified as independent risk factors for seizure relapse associated with AED withdrawal. Compared with wild type IDH1, IDH1 mutation patients had a much higher risk of relapse (hazard ratio (HR) 3.371; 95% confidence interval (CI): 0.577–6.630; p = 0.019). STR had a higher risk than GTR (HR 1.966; 95% CI: 1.363–5.122; p = 0.026). Patients treated with combined AEDs had a higher risk of recurrence than those who taking a single AED (2.369; 95% CI: 0.876–4.376).

3.4. Risk of seizure relapse increases with the number of risk factors per patient

For this group of 91 patients, the relapse rate of seizure due to AED withdrawal during 1-year follow-up was calculated according to the number of different risk factors per patient. Fig. 2 shows that 60.0% (39/65) of the patients with one or more risk factors remained seizure-free, 39.5% (15/38) of patients with 2 or more risk factors remained seizure-free, while only 28.6% (4/14) patients with all 3 risk factors remained seizure-free. Therefore, the proportion of patients with seizure relapse increased according to the number of risk factors per patient (Fig. 2).

In order to determine the statistical threshold of the number of risk factors associated with the seizure relapse due to AEDs withdrawal, an ROC curve was plotted according to seizure relapse status. The optimal threshold is the point closest to the top left corner, with the highest sensitivity and the lowest value for 1 – specificity. This point occurs at a sensitivity of 0.821 and 1 – specificity of 0.238, the biggest Yuden Index is 0.583, which corresponds to a number of risk factors of 1.5 (Fig. 3). The ROC curve indicated that the area under the curve for the number of risk factors tested was 0.815 (95% CI 0.717–0.912, P = 0.000). The above data indicates that if the number of risk factors is larger than 1.5 (i.e. 2 or more),

Table 2
Seizure status 6 and 12 months after AEDs withdrawal.

Groups	First 6 months	Last 6 months	x^2/t	p
Seizure-free	71	63	6.078	0.014
Relapsed	20	28		

Table 3
Multivariate analysis of risk factors for seizure recurrence predicted by Cox proportional hazard model.

Variable	p value	HR	95% CI
Tumor location	0.263	2.564	0.447–13.168
Multiple types of seizure	0.813	3.718	1.369–9.217
Subtotal resection	0.026	1.966	1.363–5.122
IDH1mutation	0.019	3.371	0.577–6.630
Combination of AEDs	0.037	2.369	0.876–4.376

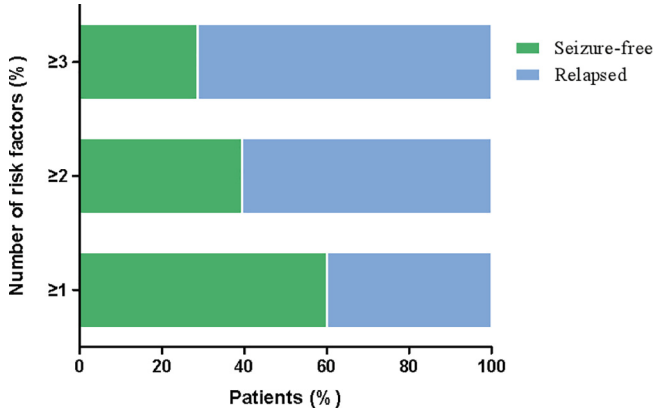

Fig. 2. Effect of the number of independent risk factors per patient on seizure relapse rate after AEDs withdrawal. Patients had no seizure for 2 years and were followed up for one year after AEDs withdrawal. Independent risk factors included subtotal resection, IDH1 mutation, and combination of AEDs. Patients were categorized into groups according to number of risk factors for seizure relapse.

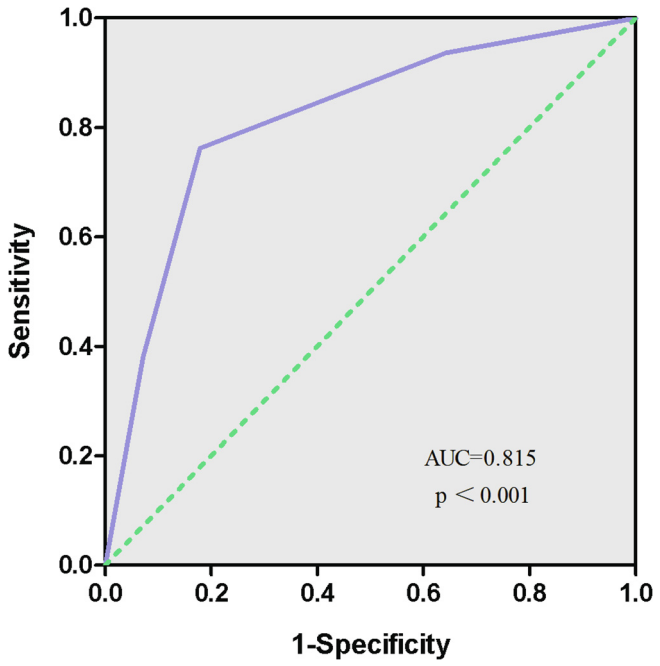

Fig. 3. Receiver operator curve for the number of risk factors. The false-negative rates and sensitivity in determining seizure relapse were plotted for each value of the number of risk factors in an ROC curve (blue). The comparison diagonal line represents a "random guess" outcome curve (green). The optimal diagnostic point is one that has the lowest false-negative value and maximal sensitivity, which is the point closest to the top left corner of the graph.

patients are more likely to have seizure relapse within 1 year after withdrawal of AEDs; and if the number of risk factors is less than 1.5 (i.e. 0 or 1), patients are more likely to experience a seizure-free outcome.

4. Discussion

In this study, we aimed to explore the short-term outcome and risk factors of seizure relapse in glioma patients after AEDs withdrawal. Our study found that the seizure recurrence rate associated with AEDs withdrawal was 30.8%, which was consistent with the recurrence rate found elsewhere [8]. Many studies have confirmed that the majority of relapse occurr in the first year [9,10]. In our study, we found that 71.4% of relapse occurred in the first 6 months after withdrawal, which is consistent with literatures.

The relationship between IDH1 mutation status and seizure recurrence in glioma patients has been explored in many studies in recent years. And there is increasing evidence that genetic biomarkers are associated with glioma-related epilepsy. Previous studies have demonstrated that IDH1 gene mutation is strongly associated with the better prognosis of glioma [11]. In addition, a retrospective study by Liang et al. showed that the presence of mutant IDH1 was the strongest predictor of postoperative seizure [12]. Furthermore, Liubinas et al. found that IDH1-R132H mutation was more common in low-grade glioma patients with seizures than in those without seizures [13]. Previously, the relationship between IDH1 mutation and drug withdrawal related seizures remains unexplored. Here, we found a strong correlation between IDH1 mutantion and seizure outcome after AEDs withdrawal in post-operative glioma patients (p = 0.001). In multivariate analysis, IDH1 mutational status was an independent predictor of seizure relapse with an HR of 3.371 (95% CI = 0.577–6.630). This result shows a high risk of recurrence associated with drug withdrawal in glioma patients with IDH1 mutation. Thus, we propose that IDH1 mutant plays a significant role in the pathogenesis of glioma associated epilepsy. Our results support further studies on the role of IDH1 mutation as a biomarker for glioma associated epilepsy and the potential for an antiepileptic therapeutic effect of IDH1 inhibitors.

Surgical treatment of tumor associated epilepsy is often recommended. Previous studies have shown that surgical resection of the lesions can help to control epilepsy of low-grade gliomas, and several analyses have shown that GTR could be used as an important predictor of seizure-free condition [14]. However, there is no study to confirm whether this benefit will extend upon the withdrawal of AEDs. Our findings suggest that STR is an independent risk factor for recurrence associated with AEDs withdrawal, with a relapse HR of 1.966 (95% CI = 1.363–5.122). This conclusion is consistent with relevant studies which highlight the importance of resection extent, considering the recurrence of gliomas and epilepsy seizures [15,16]. Therefore, patients with subtotal resection of gliomas should consider avoiding discontinuation of AEDs treatment because of the high risk of seizure relapse.

In our study, combined use of AEDs was another risk factor associated with seizure relapse after the withdrawal of AEDs. It has been reported that more than 65% of seizures could be controlled by prescribing a single AED [17]. Although there is no ultimate definition of intractable epilepsy, patients who receive more than one AED treatment are more likely to relapse during the withdrawal [18]. The odds ratio of relapse in glioma patients who need combined use of AEDs was 2.369 (95% CI = 0.876–4.376). This finding is in line with a previous study [19]. In general, the number of AEDs used to control seizures prior to withdrawal could be used as an independent predictor of seizure relapse [4]. Therefore, we should take a very cautious attitude towardspatients who are undergoing multiple AEDs treatment.

Patients with multiple types of seizure might indicate the complexity of seizures, while seizure type has previously been reported to be a neglected risk factor associated wiht AEDs withdrawal [19]. In our study, univariate analysis showed that the occurrence of multiple seizure types was associated with seizure relapse compared with single type cases ($p = 0.040$), but there was not statistically significance in multivariate analysis. Lesions in the frontal or temporal lobes seemed to be associated with the postoperative seizure relapse associated with AEDs withdrawal [20], which might be taken into account when a decision on withdrawal is required. However, in multivariate analysis, this was not an independent risk factor for seizure recurrence.

IDH1 mutation, subtotal resection, and combined use of AEDs were independent risk factors for seizure relapse in patients who had gliomas with seizures. The number of risk factors per patient should also be considered before discontinuation of AEDs. Some reports indicate that a 2- year seizure-free interval is sufficient to warrant AEDs withdrawal, while prolonging the seizure-free interval before AEDs withdrawal would not reduce the risk of recurrence [21–23]. Nevertheless, some studies have shown that prolonging seizure-free status before AEDs withdrawal may increase the possibility of seizure-free status after withdrawal. A recent *meta*-analysis showed that 2 years is the shortest interval and it is worth noting that "every additional year without seizures reduces the risk" [4]. Our results suggest that the duration of antiepileptic therapy should be prolonged appropriately for glioma patients with independent risk factor for relapse. More specifically, patients with at least two of the three independent risk factors mentioned above are much more likely to relapse than patients with only one risk factor, and the withdrawal of AEDs should be delayed accordingly.

In our study, age at onset of epilepsy, gender, family history of seizure, tumor grade, molecular pathological result of 1p/19q codeletion and MGMT promoter methylation, postoperative radiotherapy, temozolomide chemotherapy, tumor recurrence, and EEG results before AEDs withdrawal were not associated with recurrence risk. Information related to the history of seizures, such as the seizure frequency and family history, may be affected by the nature of the retrospective study. Abnormal EEG before the AEDs withdrawal indicated the risk of seizure relapse. A relevant *meta*-analysis showed that the predictive value of EEG abnormal result before AEDs withdrawal, epileptic waves in multiple regions, especially paroxysmal abnormalities, were associated with a greater risk of relapse [24]. However, it has been suggested that abnormal EEG should not be considered as an independent risk factor for seizure recurrence. More importantly, the EEG results should be classified into interictal epileptiform discharges, focal bradycardia and diffuse bradycardia (or the presence of interictal epileptiform discharges and non-epileptiform abnormalities), and we failed to record the detailed information related to the EEG result. In our study, we did not find a predictive effect of EEG results. Surprisingly, there was significant difference between low-grade gliomas and high-grade gliomas in terms of postoperative epileptic recurrence, which has been reported in the relevant literature [25]. This may be because our study is limited to WHO I-III gliomas. In addition, our results suggested that tumor recurrence was not associated with seizure relapse, while earlier studies have confirmed the relationship between postoperative seizure relapse and tumor progression [26]. This difference may be due to our small sample size and from a single center.

This retrospective study has some limitations. First, there may be a lack of detailed information, such as the frequency of seizures after surgery, and memory bias may occur because the study is retrospective rather than prospective. Secondly, this is a single-center retrospective study which is limited to 91 patients, so it is not representative to some extent. Third, the follow-up time is only one year, so these are short-term results after AEDs withdrawal. Although the rates for the first 6 months and the last 6 months are different, we do not recommend continuing to use AEDs. An extended follow-up might be more representative for seizure-free patients with WHO I-III glioma. Hence, considering the limited number of patients in this study, our results need to be validated with more patients, preferably in a multicenter study.

In conclusion, this study suggests that most seizure relapse cases occurred within the first 6 months after the first AEDs withdrawal. Subtotal resection of gliomas, IDH1 gene mutation and combined use of AEDs were independent risk factors for seizure relapse within 1 year. Once the patients had two or more independent risk factors, the probability of seizure relapse is high. We suggest prolonging the interval of seizure free before drug withdrawal can obtain better seizure free results.

Authors contribution

Jiang Hongxiang and Deng Gang contributed equally to this article and were co-authored as the first author. Dr. Hongxiang Jiang conceptualized and designed the study. Dr. Gang Deng collected and analyzed the data. Dr. Jing Cheng followed up on the patients. Dr. Hongxiang Jiang edited the pictures. Professor Qianxue Chen supervised the study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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