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A novel nomogram for predicting the risk of epilepsy occurrence after operative in gliomas patients without preoperative epilepsy history

Si-Pei Pan [a], Xiao-Lu Zheng [a], Nan Zhang [a], Xiao-Min Lin [b], Ke-Jie Li [c], Xiao-Fang Xia [c], Chang-Lin Zou [c], Wen-Yi Zhang [c,*]

[a] Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, WenZhou, China
[b] Department of Neurology, The People's Hospital of Wencheng, WenZhou, China
[c] Department of Radiotherapy, The First Affiliated Hospital of Wenzhou Medical University, WenZhou, China

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ABSTRACT

Objective: Epilepsy is a common complication in glioma patients after undergoing brain tumor surgery combined with chemotherapy and/or radiotherapy. Whether antiepileptic drug prophylaxis could be used in these patients remains an open question. The purpose of this study was to produce a model for predicting the risk of epilepsy occurrence in such patients.

Methods: The clinicopathologic data of glioma patients after tumor treatment were reviewed in this study. Univariate and multivariate logistic regression analyses were carried out to analyze the correlation between the clinicopathologic data and the risk of epilepsy occurrence. A nomogram was built according to the multivariate logistic regression model results.

Results: A total of 219 patients with gliomas were reviewed. Univariate analyses revealed that age, WHO glioma classification, CD34, EGFR, Ki67, MGMT, P53 and VIM were significantly associated with the risk of epilepsy occurrence. Multivariate analyses revealed that age, WHO glioma classification, CD34, EGFR, MGMT, and VIM were predictors of risk of epilepsy occurrence. A nomogram of the risk of epilepsy occurrence was built based on statistically significant variables from the multivariate logistic regression analysis. The c-index of the nomogram was 0.755 (95 % confidence interval (CI), 0.742–0.769).

Significance: This nomogram model provides reliable information about the risk of epilepsy occurrence for oncologists and neurological physicians.

1. Introduction

Glioma is the most common neoplasm of central nervous system (Mesfin and Al-Dhahir, 2020). Current therapeutic methods for gliomas primarily include surgery combined with chemotherapy and/or radiotherapy (Ghotme et al., 2017). Epilepsy is a common complication for glioma patients (van Breemen et al., 2007). Whether antiepileptic drug prophylaxis could be used in brain tumor patients without a history of epilepsy after treatment remains an open question. A meta-analysis (Joiner et al., 2018) demonstrated that perioperative antiepileptic drug prophylaxis for brain tumor patients undergoing surgery resulted in a statistically significant reduction in the risk of early postoperative epilepsy compared with that in controls. In a previous study of convexity meningioma patients undergoing tumorectomy, no statistical significance was found between the rate of new epilepsy in patients with the routine use of prophylactic antiepileptic drugs and the rate in untreated patients (Sughrue et al., 2011). This study called into question whether antiepileptic drugs were worth using given their cost and side effects (Sughrue et al., 2011).

The main aim of this study was to produce a novel model for predicting the risk of epilepsy occurrence in glioma patients after undergoing standard treatments. Our model focused exclusively on the risk of epilepsy occurrence in glioma patients. According to the 2016 World Health Organization (WHO) Classification of Central Nervous System Tumors, molecular subgroups could define the prognosis and treatment response of glioma patients (Kern et al., 2020). Therefore, this study used molecular markers to evaluate the risk of epilepsy occurrence in glioma patients after undergoing standard treatments. A nomogram provided a statistical model that combined multiple variables to evaluate individualized risk probabilities (Han et al., 2020). This statistical

* Corresponding author.
E-mail address: zwymike@163.com (W.-Y. Zhang).

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model presented as a nomogram could be useful to oncologists and neurological physicians for making a decision on whether to use prophylactic antiepileptic drugs.

2. Patients and methods

2.1. Study population

This retrospective study was approved by the ethics committee of the hospital, and written informed consent was obtained from all patients. From January 2010 to July 2018, glioma patients who underwent surgery were reviewed. The eligibility criteria for review were as follows: 1) underwent surgery for gliomas; 2) diagnosis confirmed by pathology; 3) no preoperative history of epilepsy; and 4) untreated by prophylactic antiepileptic drugs.

2.2. Patient characteristics

The pathological diagnosis was classified according to WHO glioma classification (Grade I to IV). CD34, CD56, Cancer germline Antigen (CgA), Epidermal Growth Factor Receptor (EGFR), Epithelial Membrane Antigen (EMA), Glial Fibillary Acidic Protein (GFAP), Isocitrate dehydrogenase1 (IDH1), Ki67, O6-methyl-guanine-DNA methyltransferase (MGMT), Oligodendrocyte Lineage Transcription Factor-2 (Olig-2), S-100, P53, Vimentin (VIM) and Synaptophysin (SYN) in tumor tissue were observed with immunohistochemical staining. Immunohistochemical staining results of Ki67 and MGMT are presented as percentages of positive cancer cells. Immunohistochemical staining results of CD34, CD56, CgA, EGFR, EMA, GFAP, IDH1, Olig-2, S-100, P53, VIM and SYN are presented as staining intensities (negative, weak positive, medium positive or strong positive). Negative (-) was defined as less than 5% of cancer cells being positive. Weak positivity (+) was defined as more than 5% and less than 30 % of cancer cells being positive. Medium positivity (++) was defined as more than 31 % and less than 50 % of cancer cells being positive. Strong positivity (+++) was defined as more than 51 % of cancer cells being positive.

2.3. Follow-up

Each patient was followed-up at every 3-month interval for the first 2 years, at every 6-month interval for the next 3 years and annually thereafter. The follow-up evaluations took place with oncologists and neurological physicians. History of epilepsy, physical examination, blood count examination, hepatic and renal function, and head MRI were determined/performed during follow-up.

2.4. Statistical analyses

Univariate and multivariate logistic regression analyses were used to assess the association of epilepsy with clinicopathologic characteristics, including age, sex, WHO glioma classification, tumor site, lobe, adjuvant radiotherapy, adjuvant chemotherapy, CD34, CD56, CgA, EGFR, EMA, GFAP, IDH1, Ki67, MGMT, Olig-2, S-100, P53, VIM and SYN. The nomogram was based on multivariable logistic regression models. Calibration curves were drawn to evaluate the consistency between the actual rate of epilepsy risk and the predicted probabilities of epilepsy risk. The distinction of the nomogram for predicting epilepsy risk was appraised by the concordance index (C-index). Univariate and multivariate logistical regression analyses were carried out using Statistical Package for Social Sciences (SPSS) version 23.0. The nomogram and calibration curves were generated with R statistical software (version 2.8.1, the rms package).

3. Results

A total of 219 glioma patients (97 female, 122 male) were reviewed in this study. The median follow-up duration was 14 months (range: 3–98 months). 59 patients (26.9 %) had epilepsy during the follow-up period. Grade II gliomas included 19 (8.7 %) diffuse astrocytomas, 4 (1.8 %) oligoastrocytomas and 15 (6.8 %) oligodendrogliomas; Grade III gliomas included 10 (4.6 %) anaplastic oligodendrogliomas, 7 (3.2 %) anaplastic astrocytomas and 2 (0.9 %) anaplastic oligoastrocytomas; and Grade IV gliomas included 162 (74.0 %) glioblastomas. Patient characteristics and immunohistochemical analysis results are shown in Table 1.

Univariate logistic regression analysis showed that age, WHO glioma classification, CD34, EGFR, Ki67, MGMT, P53 and VIM were significantly associated with epilepsy. Multivariate logistic regression analysis showed that age (OR 0.967 [95 % CI 0.940−0.995], p = 0.019), WHO glioma classification (OR 0.436 [95 % CI 0.238−0.800], p = 0.007), CD34 (OR 16.922 [95 % CI 3.208−89.275], p = 0.001), EGFR (OR 2.239 [95 % CI 1.347−3.722], p = 0.002), MGMT (OR 1.019 [95 % CI 1.002−1.036], p = 0.025) and VIM (OR 0.362 [95 % CI 0.135−0.974], p = 0.044) were predictors of epilepsy. The univariate and multivariate logistic regression models for the prediction of epilepsy are shown in Tables 2 and 3.

Then, as shown in Fig. 1, a nomogram was established to predict the risk of epilepsy occurrence according to the multivariate logistic regression analysis on the basis of statistically significant variables. The variables that increased the probability of epilepsy risk included younger age at diagnosis, lower-grade tumor, higher expression intensity of CD34, EGFR and MGMT in tumor tissue detected by using immunohistochemistry, and lower expression intensity of VIM in tumor tissue detected by using immunohistochemistry. The C-index of this nomogram for predicting epilepsy risk was 0.755 (95 % confidence interval (CI), 0.742–0.769). Moreover, the calibration curve showed that there was good agreement between the bias-corrected curve and the ideal curve (Fig. 2).

4. Discussion

Nomograms have the ability to provide single numerical models to predict the probability of an event, such as death, occurrence or recurrence (Iasonos et al., 2008). An independently validated nomogram was developed using TCGA data and OBTS data to predict the probability of survival for lower-grade glioma patients (Gittleman et al., 2019). Nomograms were built to predict the overall survival of high-grade glioma patients (Xia et al., 2020). A prognostic nomogram model was built to predict the overall survival of glioma patients (Zeng et al., 2020). However, no study to date has built a nomogram to predict the probability of epilepsy risk. This study used molecular markers in tissue to build a nomogram for predicting the risk of epilepsy occurrence in glioma patients after tumor treatment.

The results of our study demonstrated that patients with lower-grade gliomas had epilepsy more frequently. Three patients with gangliglioma (WHO Grade I) had epilepsy during the follow-up period. Previous studies also pointed out that the rate of epilepsy was more frequent in patients with low-grade gliomas (WHO Grades I–II) than in those with high-grade gliomas (WHO Grades III–IV) (Lee et al., 2010; Rosati et al., 2009).

The results in this study demonstrated that higher expression intensity of CD34, EGFR and MGMT in tumor tissue detected by using immunohistochemistry was significantly associated with the risk of epilepsy occurrence. CD34 has been confirmed as a marker for fibrocytes, fibroblasts and neovascular endothelial cells as well as a marker for tumor invasiveness in several types of cancer cells (Ma et al., 2010; Schulze et al., 2020). CD34 was significantly overexpressed in glioma tissues and identified as a potential diagnostic and prognostic marker (Kong et al., 2016). CD34, detected in malformations of cortical development, could be identified as a marker of risk for seizure relapse after epilepsy surgery (Czornyj and Lazarowski, 2014). Similarly, this study found that CD34 could be a biomarker of risk for epilepsy occurrence in

Table 1
Patient characteristics.

Characteristic	No. of patients (%)
Total	219
Age	
Median	53.0years
Range	7–79
Sex	
Female	97(44.3 %)
Male	122(55.7 %)
WHO Gliomas Classification (pathological type)	
GradeII(diffuse astrocytoma, oligoastrocytoma, oligodendroglioma)	38(17.4 %)
GradeIII(anaplastic oligodendroglioma, anaplastic astrocytoma, anaplastic oligoastrocytoma)	19(8.7 %)
GradeIV(glioblastoma)	162(74.0 %)
Tumor site	
Left cerebral hemisphere	99(45.2 %)
Right cerebral hemisphere	105(47.9 %)
Cerebellum	2(0.9 %)
Brainstem	3(1.4 %)
Other	10(4.6 %)
Lobe	
Frontal lobe	74(33.8 %)
Temporal lobe	50(22.8 %)
Parietal lobe	12(5.5 %)
Occipital lobe	3(1.4 %)
Frontal temporal lobe	23(10.5 %)
Frontal parietal lobe	12(5.5 %)
Temporal parietal lobe	8(3.7 %)
Occipital parietal lobe	8(3.7 %)
Temporal occipital lobe	6(2.7 %)
Other	23(10.5 %)
Adjuvant radiotherapy	
Yes	109(49.8 %)
No	110(50.2 %)
Adjuvant chemotherapy	
Yes	142(64.8 %)
No	77(35.2 %)
CD34	
Negative (-)	44(20.1 %)
Weak positive (+)	168(76.7 %)
Medium positive (++)	6(2.7 %)
Strong positive (+++)	1(0.5 %)
CD56	
Negative (-)	208(95.0 %)
Weak positive (+)	11(5.0 %)
Medium positive (++)	0(0%)
Strong positive (+++)	0(0%)
CgA	
Negative (-)	218(99.5 %)
Weak positive (+)	1(0.5 %)
Medium positive (++)	0(0%)
Strong positive (+++)	0(0%)
EGFR	
Negative (-)	104(47.5 %)
Weak positive (+)	86(39.3 %)
Medium positive (++)	19(8.7 %)
Strong positive (+++)	10(4.6 %)
EMA	
Negative (-)	204(93.2 %)
Weak positive (+)	15(6.8 %)
Medium positive (++)	0(0%)
Strong positive (+++)	0(0%)
GFAP	
Negative (-)	41(18.7 %)
Weak positive (+)	148(67.6 %)
Medium positive (++)	21(9.6 %)
Strong positive (+++)	9(4.1 %)
IDH1	
Negative (-)	201(91.8 %)
Weak positive (+)	13(5.9 %)
Medium positive (++)	1(0.5 %)
Strong positive (+++)	4(1.8 %)
Ki67	
Median	20 %
Range	1%-90 %
MGMT	
Median	1%
Range	0%-90 %
Olig-2	
Negative (-)	166(75.8 %)
Weak positive (+)	50(22.8 %)
Medium positive (++)	1(0.5 %)
Strong positive (+++)	2(0.9 %)
S-100	
Negative (-)	107(48.9 %)
Weak positive (+)	108(49.3 %)
Medium positive (++)	2(0.9 %)
Strong positive (+++)	2(0.9 %)
P53	
Median	0%
Range	0%-90 %
VIM	
Negative (-)	64(29.2 %)
Weak positive (+)	145(66.2 %)
Medium positive (++)	6(2.7 %)
Strong positive (+++)	4(1.8 %)
SYN	
Negative (-)	154(70.3 %)
Weak positive (+)	60(27.4 %)
Medium positive (++)	3(1.4 %)
Strong positive (+++)	2(0.9 %)

CgA: Cancer germline Antigen; EGFR: Epidermal Growth Factor Receptor; EMA: Epithelial Membrane Antigen; GFAP: Glial Fibillary Acidic Protein; IDH1: Isocitrate dehydrogenase1; MGMT: O6-methyl-guanine-DNA methyltransferase; Olig-2: Oligodendrocyte Lineage Transcription Factor-2; VIM: Vimentin; SYN: Synaptophysin.

Table 2
Univariate logistic regression analyses of the risk of epilepsy occurrence.

Variable	OR	95 %CI	*P*
Age	0.961	0.941–0.981	0.000
Sex	0.817	0.446–1.497	0.514
WHO Gliomas Classification	0.484	0.336–0.698	0.000
Tumor site	1.123	0.823–1.532	0.465
Lobe	0.918	0.828–1.019	0.108
Adjuvant radiotherapy	1.246	0.685–2.267	0.472
Adjuvant chemotherapy	1.527	0.827–2.820	0.176
CD34	15.530	3.720–64.835	0.000
CD56	1.590	0.448–5.641	0.473
CgA	0.000	0.000-∞	1
EGFR	2.493	1.688–3.682	0.000
EMA	0.397	0.087–1.814	0.233
GFAP	1.259	0.812–1.950	0.303
IDH1	1.178	0.656–2.117	0.583
Ki67	0.977	0.961–0.994	0.007
MGMT	1.030	1.017–1.043	0.000
Olig-2	1.441	0.828–2.509	0.196
S-100	1.015	0.600–1.717	0.955
P53	1.016	1.001–1.030	0.031
VIM	0.493	0.281–0.864	0.014
SYN	0.896	0.513–1.564	0.699

CgA: Cancer germline Antigen; EGFR: Epidermal Growth Factor Receptor; EMA: Epithelial Membrane Antigen; GFAP: Glial Fibillary Acidic Protein; IDH1: Isocitrate dehydrogenase1; MGMT: O6-methyl-guanine-DNA methyltransferase; Olig-2: Oligodendrocyte Lineage Transcription Factor-2; VIM: Vimentin; SYN: Synaptophysin.

glioma patients after surgery. EGFR plays a crucial role in regulating cancer cell differentiation, proliferation and migration (Wang et al., 2020). EGFR is often expressed in EGFR-amplified glioma cells and promotes tumor invasion and recurrence (Eskilsson et al., 2018). EGFR may cause tumor recurrence, which results in epilepsy occurrence. MGMT is a ubiquitous DNA repair enzyme and can rapidly reverse

Table 3
Multivariate logistic regression analyses of the risk of epilepsy occurrence.

Variable	OR	95 %CI	*P*
Age	0.967	0.940–0.995	0.019
WHO Gliomas Classification	0.436	0.238–0.800	0.007
CD34	16.922	3.208–89.275	0.001
EGFR	2.239	1.347–3.722	0.002
Ki67	0.993	0.969–1.017	0.555
MGMT	1.019	1.002–1.036	0.025
P53	1.009	0.990–1.029	0.368
VIM	0.362	0.135–0.974	0.044

EGFR: Epidermal Growth Factor Receptor; MGMT: O6-methyl-guanine-DNA methyltransferase; VIM: Vimentin.

alkylation at the O6 position (Chai et al., 2019). MGMT promoter methylation provided a benefit to glioblastoma patients from temozolomide and has been identified as a predictive marker for temozolomide sensitivity and as an independent favorable prognostic factor (Chai et al., 2019; Hegi et al., 2005). MGMT was useful for predicting glioma patients at high risk of recurrence and treatment response (Wu et al., 2019). The mechanism by which MGMT induces epilepsy may be that MGMT influences the therapeutic effect and promotes tumor recurrence.

In this study, the results demonstrated that lower expression intensity of VIM in tumor tissue detected by using immunohistochemistry was significantly associated with the risk of epilepsy occurrence. VIM, a member of the intermediate filament family, maintains cell morphology and ensures the integrity of the cytoplasm (Xue et al., 2017). In the neurological system, VIM is localized in axonal growth fronts and is related to nerve regeneration, including neuroplasticity, myelination, and kinase signaling (Sullivan et al., 2018). Therefore, higher expression of VIM could protect nerve cell integrity, which had been destroyed by treatment, and then reduce epilepsy occurrence.

To date, no study has reported that EGFR, MGMT and VIM are related to epilepsy. Our study demonstrated that these biomarkers were associated with epilepsy.

There were some limitations in our study. First, the most important limitation was that no molecular biology data provided evidence that those biomarkers were associated with epilepsy. Future research will focus on how those biomarkers affect epilepsy. Second, in our study, all biomarkers in tumor tissue were detected by immunohistochemistry. And IDH1 mutation was also detected by immunohistochemistry instead of pyrosequencing. Pyrosequencing can be used to detect IDH1 mutation more accurately. In the future, we will study the relationship between

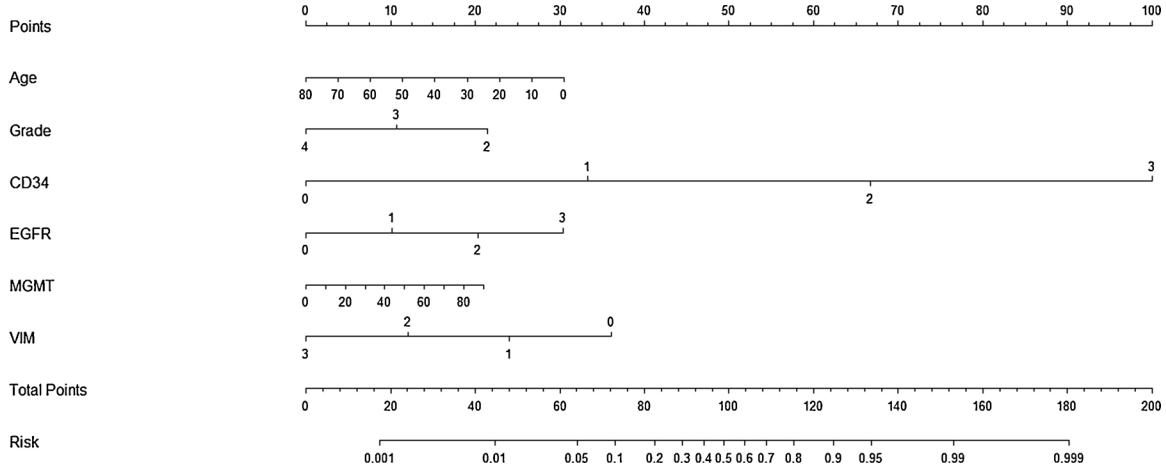

Fig. 1. A nomogram for predicting the risk of epilepsy occurrence.
Age: Unit=years.
Grade: WHO Gliomas Classification; 2=Grade II, 3=Grade III, 4=Grade IV.
CD34: 0=negative(-), 1=weak positive (+), 2=medium positive (++), 3=strong positive (+++).
EGFR: Epidermal Growth Factor Receptor; 0=negative(-), 1=weak positive (+), 2=medium positive (++), 3=strong positive (+++).
MGMT: O6-methyl-guanine-DNA methyltransferase; Unit=%.
VIM: vimentin; 0=negative(-), 1=weak positive (+), 2=medium positive (++), 3=strong positive (+++).
Risk: the probability of epilepsy risk.

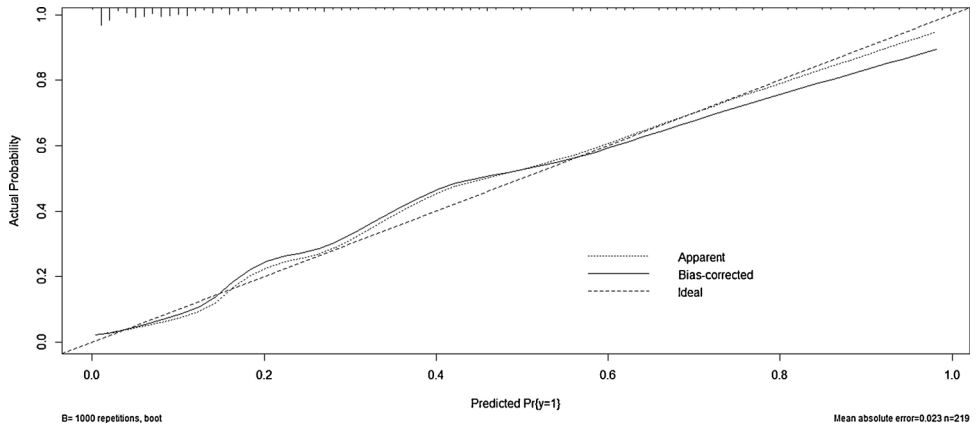

Fig. 2. Calibration curves for the risk of epilepsy occurrence.

epilepsy and IDH1 mutation detected by both immunohistochemistry and pyrosequencing. Third, this study was not a multicenter study. Next, the patients from multicenter clinics will be reviewed.

In summary, this nomogram calculated individualized epilepsy risk probabilities for glioma patients after tumor treatment and could help oncologists and neurological physicians in the decision of prophylactic antiepileptic drug use for their patients.

Declaration of Competing Interest

The authors report no declarations of interest.

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