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Development and Validation of a Nomogram for Predicting Seizure Outcomes After Epilepsy Surgery for Children with Focal Cortical Dysplasia

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ABSTRACT

AIM: To construct a prediction nomogram model for the postoperative seizure outcomes in children with focal cortical dysplasia (FCD).

MATERIAL and METHODS: We retrospectively reviewed the clinical data of 97 children with epilepsy secondary to FCD who had undergone resection surgery at Children's Hospital of Chongqing Medical University from June 2013 to September 2019. Univariate and multivariate Cox proportional hazards regression were used to explore the predictors of postoperative persistent seizure, and a nomogram prediction model for postoperative seizure outcome was developed. The C-index was chosen to evaluate the discriminability of the nomogram with internal validation. Calibration curves and decision curve analysis were used to evaluate consistency and clinical efficacy, respectively.

RESULTS: The complete resection of epileptogenic focus and the pathological type of FCD were independent predictors of persistent seizure in children with epilepsy secondary to FCD after surgery. Based on multivariate Cox proportional hazard regression, a predictive nomogram for epilepsy outcome was established and validated via the bootstrap method with 1000 resamples. The nomogram showed superior prediction accuracy (C-index = 0.883); by drawing and reviewing the calibration curve and decision curve, the nomogram presented good consistency and clinical efficacy.

CONCLUSION: A nomogram prediction model of postsurgery seizure outcome in children with epilepsy secondary to FCD was constructed based on four variables, providing a reliable and convenient tool for individual seizure outcome prediction.

KEYWORDS: Epilepsy, Focal cortical dysplasia, Nomogram, Predicting, Seizure outcome

INTRODUCTION

Focal cortical dysplasia (FCD) is a common subtype of cerebral cortical developmental malformation characterized by abnormalities in the differentiation and migration of cerebral cortical neurons (6). FCD is intrinsically epileptogenic and is the most frequent histopathology type in children with refractory epilepsy undergoing surgery. Because epilepsy secondary to FCD typically presents as refractory to medication, resection surgery is currently a widely accepted treatment option (4,8). Before 2000, only approximately 40% of FCD patients were seizure free within 1 year postoperatively (17). In recent years, the surgical outcomes of FCD patients have been improved through the use of multimodality imaging (1,5), more complete presurgical valuation, and a deeper understanding of FCD pathology (2,10), and the seizure free rate of patients with FCD within 2 years after surgery has reached approximately 55% (15). However, because a propor-

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tion of patients with FCD still have unsatisfactory outcomes after surgery, determining ideal surgical candidates and predicting their postoperative prognosis is particularly important. Currently, different centers have reported varying conclusions about the predictors of seizure free rate in patients with FCD, including whether the lesion can be detected by magnetic resonance imaging (18), whether the epileptogenic focus has been completely resected (11), the FCD pathological type (10,11), and whether FCD patients present multiple epileptic seizure types (10), among others. In the present study, we collected variables that may influence postoperative seizure outcome in patients with FCT based on the findings of previous studies, explored the predictors of these surgical outcomes, and aimed to construct a prediction nomogram model for the postoperative seizure outcomes. Because seizures recur within 6 months after surgery in more than 80% of patients with FCD, and because studies have reported that the proportion of patients who are seizure free with intractable epilepsy after surgery stabilizes after 2 years (13), we attempted to predict seizure outcomes at 6 months, 1 year, and 2 years after surgery to provide a tool for individualized clinical decision making and risk-adapted treatment after surgery in patients with FCD.

MATERIAL and METHODS

This study was approved by the Ethics Committee of Children's Hospital of Chongqing Medical University (File No. 2021.423). All data were confidential.

Patients

We retrospectively analyzed 102 consecutive children with refractory epilepsy who underwent surgical treatment and had histology-confirmed FCD at the Children's Hospital of Chongqing Medical University from June 2013 to September 2019. Inclusion criteria were 1) histologically confirmed type I, II, or III FCD and 2) postsurgical follow-up of at least 2 years. Exclusion criteria were 1) lack of complete imaging data after surgery (n=3) and 2) second surgery during the follow-up period (n=2). The collected data comprised demographic data (sex, age at surgery, age at onset, duration of epilepsy, epilepsy family history, history of febrile convulsions, presence of persistent status epilepticus, etc.), preoperative seizure condition (type of antiepileptic medications, frequency and type of seizures), preoperative evaluation (including scalp electroencephalography [EEG], video EEG, cranial magnetic resonance imaging [MRI], and alternative examinations such as fluorodeoxyglucose [FDG]–positron emission tomography [PET] and electrocorticography), and postoperative follow-up data (postoperative cranial MRI and EEG).

Presurgical Evaluation

All children underwent preoperative 1.5T or 3T brain MRI and scalp EEG. Magnetic resonance spectroscopy was performed in 47 children, and FDG-PET was performed in 26 children. MRI sequences included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR). Features considered to be associated with FCD were cortical thickening, indistinct gray–white matter junctions, subcortical high signals in the T2/FLAIR phase, abnormal brain sulci, and lobar atrophy. According to the preoperative diagnosis, we classified the cranial MRI data as follows: clear lesions on MRI (lesions clearly demonstrated, surgical site compatible with abnormal sites on MRI, and FCD identified according to preoperative MRI), detective lesions on MRI (abnormal sites on MRI compatible with surgical sites but poorly demonstrated lesions and unclear preoperative diagnosis), and occult lesions on MRI (normal brain MRI or no abnormalities at surgical site). We performed scalp EEG with reference to the international 10–20 electrode system. Fifty patients had supplemented prolonged video EEG to record at least two habitual seizures. In cases in which preoperative noninvasive examinations could not locate the epileptogenic focus or the possible involvement of functional areas was suggested, intracranial cortical electrodes were implanted. Interictal EEG spikes were defined as EEG lateral (>75% of spikes restricted to the FCD side), bilateral, and multifocal. To facilitate statistical analysis, the lateral EEG spikes were separated from the others (9). According to the form of discharges recorded by prolonged video EEG, ictal EEG patterns were grouped as regional (confined to one lobe or two adjacent sites) or not regional (multilobe, hemispheric, or generalized). Seizure semiology was classified as multiple epileptic seizure type and single epileptic seizure type. Based on the symptoms of the seizure, seizure semiology was defined as lateralized or nonlateralized. Both hypometabolic and hypermetabolic lesions on PET were regarded as abnormalities.

Surgery and Pathology

After a multidisciplinary team reached consensus regarding the multimodality evaluation, all patients underwent surgery. The surgery was approved until concordance was observed in at least two modalities (scalp EEG, video EEG, clear lesion on MRI, and localized pattern on FDG-PET). The pathological diagnosis was based on the 2011 International League Against Epilepsy (ILAE) classification system (2). Because previous studies suggested that temporal lobe lesions and multilobar lesions may affect the postoperative outcome, the FCD sites were classified as temporal or extratemporal and as single lobe or multilobar (16).

Postoperative Evaluation and Outcome

All patients underwent scalp EEG at 3 months, 6 months, and 1 year, and a brain MRI was performed at 6 months. We assessed the completeness of the resection of the epileptogenic focus based on a comparison of the postsurgical cranial MRI with the preoperative scan, and we evaluated the completeness of the resection only for patients who presented with a clear or detective lesion on the preoperative cranial MRI. Antiepileptic drug (AED) reduction was initiated when the patient was consistently seizure free and had two consecutive normal scalp EEGs. The seizure outcome was evaluated during follow-up according to the ILAE classification system as seizure free (ILAE class I + II) and persistent seizures (19). Patients who were seizure free postoperatively and had seizures during the planned AED reductions, but who remained seizure free after AED restoration, were considered to have persistent seizures. We recorded the time of the first seizure. Postoperative

assessment was based on the clinical medical records of 87 patients and on telephone follow-up of 10 patients.

Statistical Analysis

We applied SPSS 22.0 and R 4.0.2 software for statistical analysis. Continuous variables are expressed as the mean ± standard deviation, and categorical variables are described as numbers (percentages). To choose the prognostic variables, univariate Cox regressions were constructed with a *p* value threshold of 0.05. Variables with a p value <0.05 in the univariate Cox regression were then included in a multivariate analysis. Hazard ratios (HRs) were calculated via univariate Cox regression analysis and expressed as 95% confidence intervals (CIs). We constructed a multivariate Cox proportional hazard model using the "enter" regression procedure. A nomogram was developed based on the results of the multivariable Cox regression. We calculated the C-index to evaluate the discriminability of the nomogram through a bootstrap method with 1,000 resamples. By evaluating the consistency between the predicted seizure free probability and the actual seizure free proportion, we plotted a calibration curve to assess the consistency of the prediction nomogram. To calculate the net benefit at each risk threshold probability to evaluate the clinical utility of the nomogram, we used decision curve analysis. The R packages "survival" and "rms" were used to develop and validate the nomogram. For all statistical testing, a two-sided significance level (alpha) of 0.05 was chosen.

RESULTS

Patient Characteristics

Ninety-seven children with epilepsy secondary to FCD were included in the present study, and their characteristics are summarized in Table I. The follow-up time ranged from 24 months to 113 months (median: 37 months). Female patients accounted for 47 (48.5) of the patients in the cohort. The most frequent pathological type in the cohort was FCD type II, accounting for 55 (56.7) patients, with 21 (21.6%) each with FCD type I and FCD type III. MRI was able to detect FCD lesions in 76 (78.4%) patients and complete resection of epileptogenic focus in 60 (75%) patients; 38 (39.2%) patients had persistent seizures, and 59 (60.8%) were seizure free at the latest follow-up. Forty (46.2%) patients were seizure free after a reduction in antiepileptic drugs.

Nomogram Model for Seizure Outcome

Comparison of patient data between the patients who were seizure free and those with persistent epilepsy suggested that the statistically significant (p<0.05) factors in the univariate Cox regression were whether the lesion was detected on MRI, whether the FCD lesion was completely resected, the pathological type of FCD, and whether the lesion was in the temporal lobe, as detailed in Table I. Based on the results of the univariate Cox regression analysis, these four variables were included in a multivariate Cox proportional hazard model via the "enter" procedure, and the analysis showed that in children with FCD, complete resection of the FCD lesion and type of FCD pathology were independent predictors of persistent seizures after surgery (as detailed in Table II). In the development and validation of the nomogram prediction model, we constructed a nomogram prediction model integrating the aforementioned four significant variables (Figure 1). The nomogram assigned scores according to the contribution of each variable to the seizure outcome after surgery. By summing the assigned

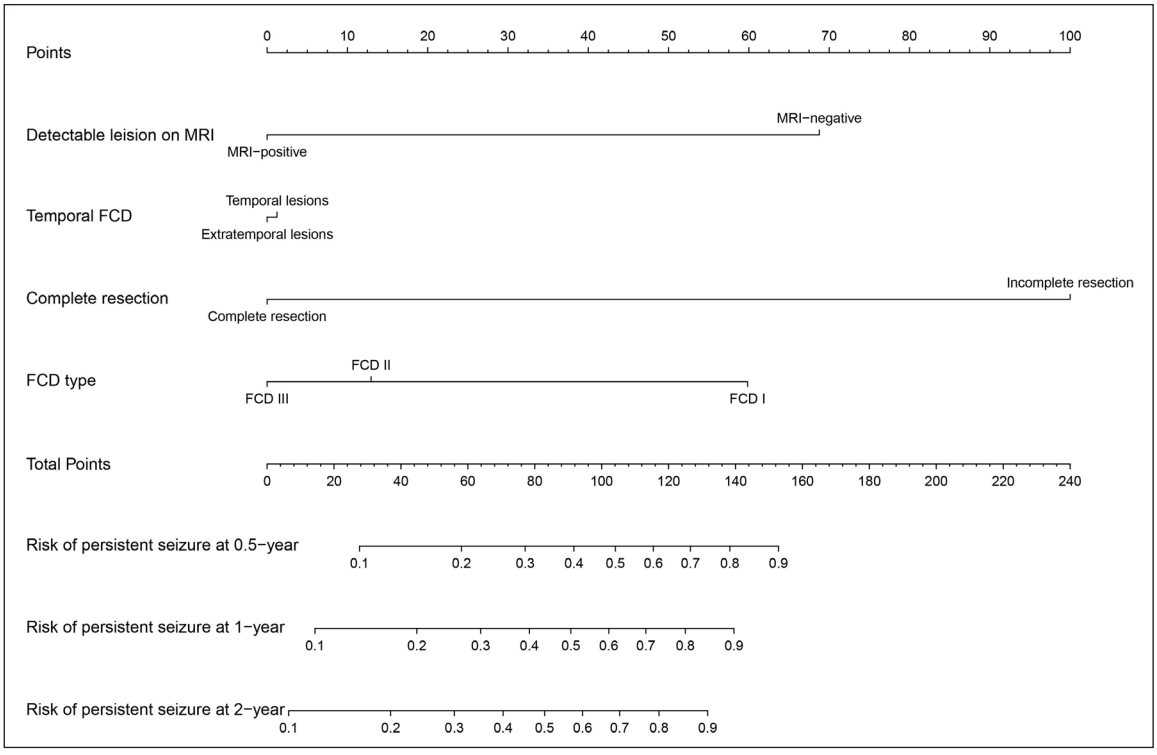

Figure 1: Nomogram for predicting seizure outcomes after epilepsy surgery for children with focal cortical dysplasia.

Table I: Demographic Characteristics and Presurgical Evaluations of 97 Children with FCD

Variable	Patients (n=97)	Seizure free (n = 59)	Persistent seizures (n=38)	Hazard ratio	p
Women	47 (48.5)	27 (45.8)	20 (52.6)	1.20	0.56
Age at surgery, months	78.3 ± 43.3	81.9 ± 44.3	72.8 ± 41.6	1.00	0.94
Age at onset, months	61.5 ± 39.0	65.2 ± 40.2	55.7 ± 36.8	1.00	0.98
Duration of epilepsy	17.7 ± 22.2	18.0 ± 20.8	17.2 ± 24.5	1.00	0.93
Family history	6 (6.2)	2 (3.4)	4 (10.5)	2.36	0.11
Febrile convulsion	8 (8.2)	2 (3.4)	6 (15.8)	1.03	0.97
Status epilepticus	11 (11.3)	8 (13.6)	3 (7.9)	0.44	0.63
Delayed development	21 (21.6)	9 (15.3)	12 (31.6)	1.89	0.69
Seizure frequency				1.02	0.92
Daily	30 (30.9)	19 (32.2)	11 (28.9)		
Weekly	18 (18.6)	10 (16.9)	8 (21.1)		
Monthly to yearly	49 (50.5)	30 (50.8)	19 (50.0)		
Multiple seizure types	32 (33.3)	20 (33.9)	12 (31.6)	0.93	0.84
Monotherapy	29 (29.9)	18 (30.5)	11 (28.9)	1.02	0.92
Lateralized semiology	33 (34.0)	20 (33.9)	13 (34.2)	1.12	0.74
Lateralization on interictal EEG	72 (74.2)	47 (79.7)	25 (65.8)	0.58	0.12
Regional pattern on ictal EEG (n=49)	34 (69.4)	21 (67.7)	13 (72.2)	1.31	0.61
Detectable lesion on MRI	76 (78.4)	54 (91.5)	22 (57.9)	0.25	**<0.001***
Clear lesion on MRI	50 (51.5)	35 (59.3)	15 (39.5)	0.53	0.58
Lesion on magnetic resonance spectroscopy (n=47)	32 (68.1)	19 (67.9)	13 (68.4)	0.92	0.87
Focal abnormal metabolism on PET (n=26)	20 (76.9)	11 (84.6)	9 (69.2)	0.66	0.49
Intracranial EEG	26 (26.8)	14 (23.7)	12 (31.6)	1.50	0.24
Temporal FCD	40 (41.2)	30 (50.8)	10 (26.3)	0.42	**0.02***
Multilobar FCD	12 (12.4)	8 (13.6)	4 (10.5)	0.78	0.64
FCD type					**<0.001***
II to I	21 (21.6)	5 (8.5)	16 (42.1)	0.28	**<0.001**
III to I	55 (56.7)	37 (62.7)	18 (47.4)	0.15	**0.001**
II to III	21 (21.6)	17 (28.8)	4 (10.5)	1.87	0.26
Complete resection (n = 80)	60 (75.0)	51 (94.4)	9 (34.6)	0.08	**<0.001***

***statistically significant difference between the variables.*

Table II: Multivariate Cox Proportional Hazards Regression Analysis for Persistent Seizure

Variable	HR	95% CI	p
Detectable lesion on MRI	0.34	0.08–1.46	0.15
Temporal FCD	1.00	0.40–2.51	0.99
Complete resection	0.09	0.04–0.24	**<0.001***
FCD			**0.04***
FCD II versus FCD I	0.33	0.13–0.85	**0.02***
FCD III versus FCD I	0.25	0.07–0.91	**0.04***
FCD II versus FCD III	1.34	0.41–4.40	0.63

***statistically significant difference between the variables.*

scores, we obtained the total score, which corresponds to the risk of persistent seizures after FCD surgery. We calculated the C-index of 0.88 (95% CI: 0.85–0.95) via the bootstrap method with 1000 resamplings, indicating that the model had good discriminability. Calibration curves were plotted to compare the predicted probability with the actual observed probability. The calibration curves at 6 months, 1 year, and 2 years of persistent seizures showed favorable consistency (Figure 2). Figure 3 shows the decision curves, which indicate that the nomogram had good clinical efficacy. Because the nomogram model incorporated only four variables, we did not develop a novel risk grouping.

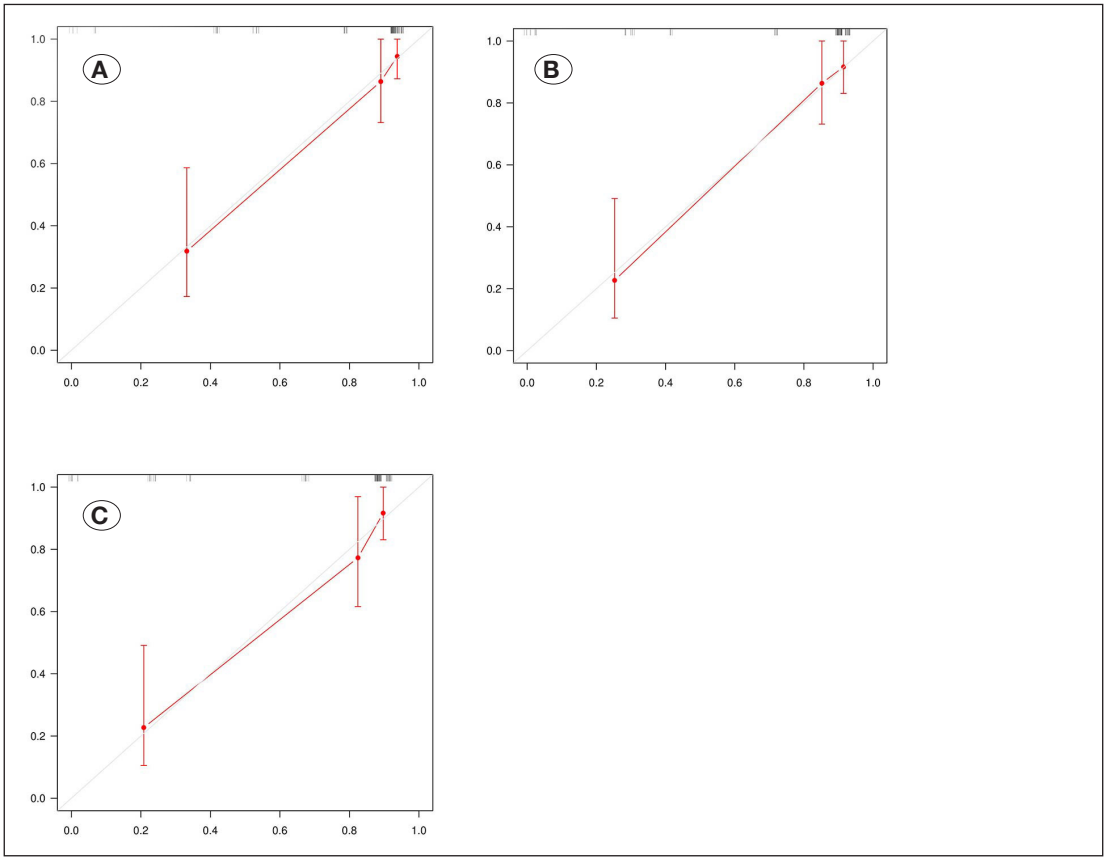

Figure 2: Calibration curve of predicted seizure outcome at six months, one year and two years after surgery.

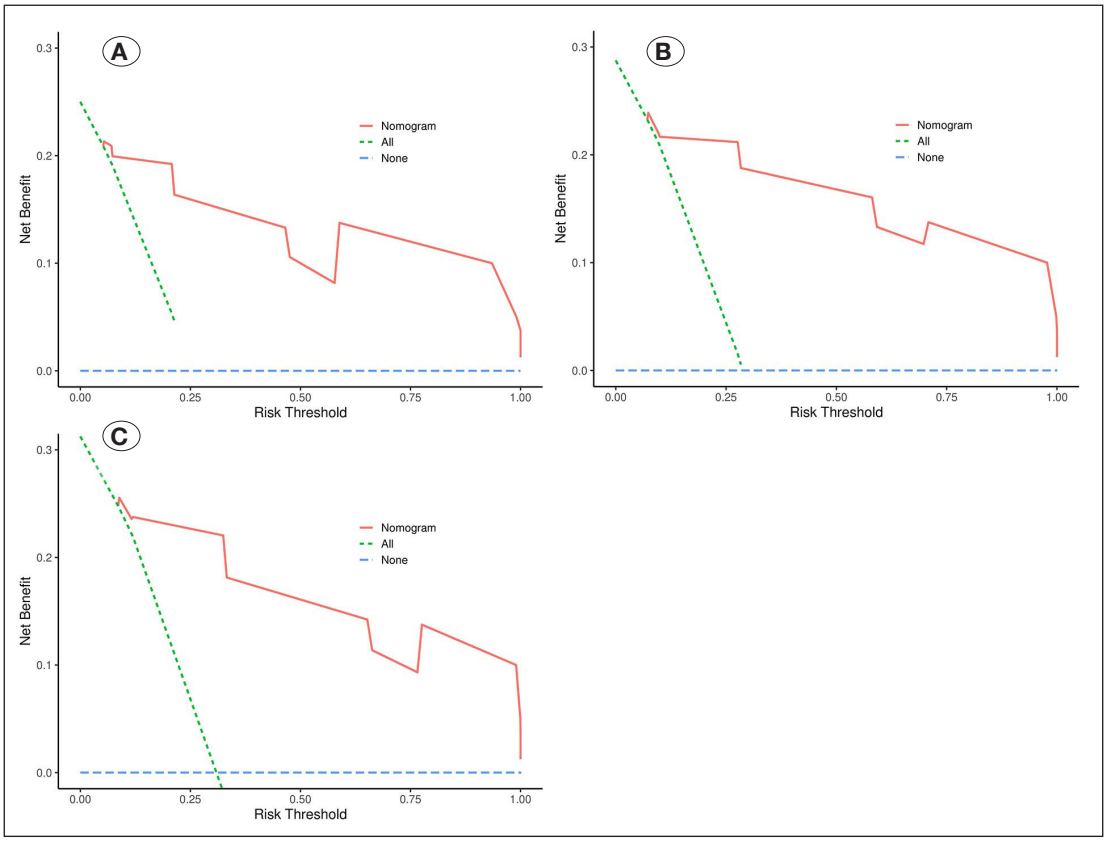

Figure 3: Clinical decision curve for predicting postoperative seizure outcomes in children with focal cortical dysplasia.

DISCUSSION

The present study analyzed the predictors of seizure outcomes after surgery in children with epilepsy secondary to FCD in a single-center cohort and developed and validated a prognostic tool based on preoperative brain MRI and postoperative pathological type. This nomogram has clinical value in postoperative risk stratification, and the predicted seizure outcomes can be used as a basis for individualized treatment decision making and risk-adapted treatment. The rate of seizure recurrence after 2 years was very low (only 5.2%), and the median time to occurrence of seizure was 4 months, which is consistent with previous reports (7), suggesting that the 2-year risk of persistent seizures predicted by our nomogram can, to a certain extent, substitute for long-term seizure outcomes.

Complete resection of FCD lesions and type of FCD pathology were independent predictors of seizure outcomes. It is now generally accepted that complete lesion resection is the primary condition for postoperative seizure control and that seizures depend on the size of the residual lesion. This is because changes in the area around the lesion continue for up to several years until the seizure activity of the residual lesion exceeds a threshold, after which clinically visible seizures reoccur. In addition, the pathological type of FCD also affects seizure outcomes after surgery. We also found better seizure control in patients with FCD type II and FCD type III than in patients with FCD type I, although there was no significant difference between patients with FCD type II and FCD type III (detailed in Figure 4). In another cohort that included 40 children with FCD, the postoperative seizure free rate of epilepsy was 75% for patients with FCD type II versus only 21% for patients with FCD type I (12). On one hand, this may be because FCD type I is associated with the most mild pathological changes, which are hard to detect by MRI (16), whereas on the other hand, FCD type I has more diffuse and extensive lesions, resulting in the lesion not being easily completely removed in surgery (3).

Many previous studies have concluded that the presence of MRI-positive lesions is an important predictor of seizure outcome after FCD surgery, and a recent meta-analysis also found that patients with detectable lesions on MRI had a 2.5 times greater rate of being seizure free than patients with occult lesions on MRI (18). Based on these discoveries, our study further explored the effect of MRI lesion clarity on seizure outcome by grouping the patients into those with clear lesions on MRI, detectable lesions on MRI, and occult lesions on MRI, and we found that the effect of lesion detectability was greater than that of lesion clarity on MRI. However, we suppose that the impact of the detection of lesions on MRI on seizure outcome depends on whether other alternative imaging examinations have been performed. We speculate that precise localization of epileptogenic focus can still be achieved based on other alternative imaging examinations. For example, because of the low neuronal activity of FCD, some mild FCD lesions may be missed by MRI but present as hypometabolic regions on FDG-PET (5). Single-photon emission computed tomography can detect some very small changes due to the three-times blood perfusion in the abnormal region during seizures (1). In a recent study by Seong et al., after all patients had undergone FDG-PET and invasive EEG, 60% of patients in both the MRI-detected lesion group and the MRI-occult lesion group achieved seizure free status (16). Thus, we hypothesized that for patients with occult MRI lesions, the key to postoperative

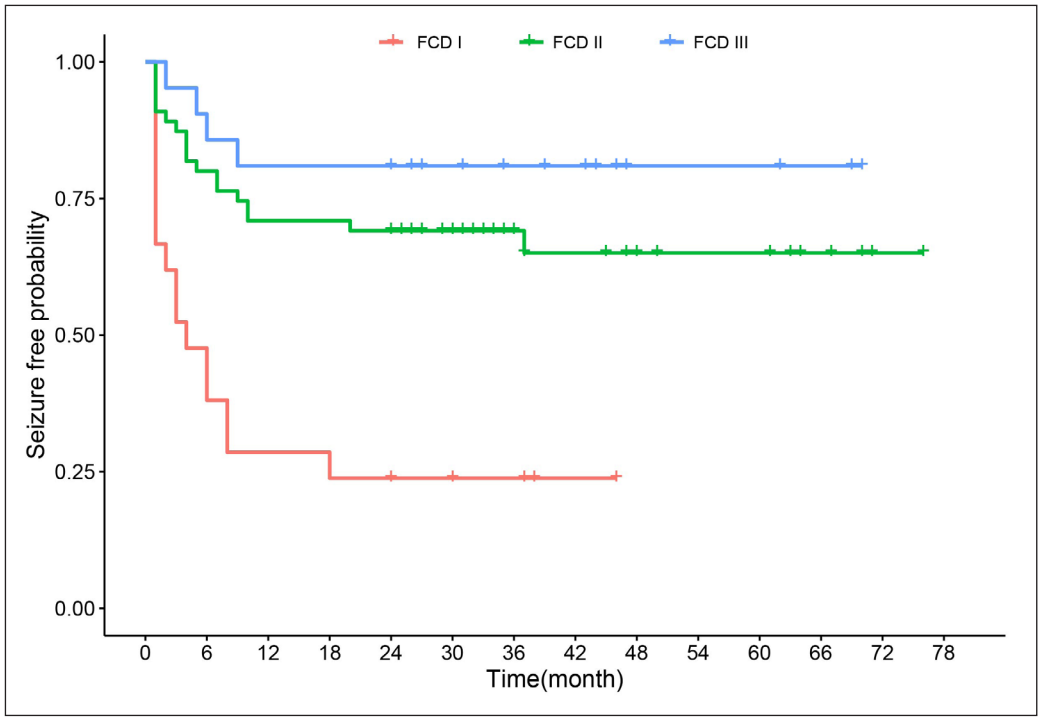

Figure 4: Comparison of seizure-free proportion after surgery in children with focal cortical dysplasia among different pathological types.

seizure control was alternative imaging examinations; however, we ultimately incorporated MRI-detected lesions in the construction of the nomogram. Because other imaging examinations such as FDG-PET were not routinely performed in our cohort, we obtained an idea derived from Rathore and Radhakrishnan (14), who argued that surgical treatment planning in developing countries should be customized based on medical resources and not just replicate epilepsy treatment protocols used in Western countries. Because the routine use of expensive invasive EEG assessment is undoubtedly difficult in countries with limited medical resources, we finally decided to include it in the prediction nomogram model. This also suggests that our model has a higher value in low- and middle-income countries.

Limitations

Our study has several limitations. This study was a retrospective, single-center study with a limited sample size, and thus, requires validation by multicenter prospective studies in the future. Two important variables in the prediction nomogram model, whether the lesion can be detected on MRI and the completeness of epileptogenic focus resection, are somewhat subjective, which could lead to bias during the application of the nomogram model and requires establishing a more standardized and quantitative evaluation in future studies. Because of the insufficient sample size, external validation of this nomogram prediction model for the postsurgical seizure outcome of FCD in children was unavailable.

CONCLUSION

Our study revealed that complete resection of epileptogenic focus and pathological type of FCD were independent predictors of seizure outcome after resection surgery in children with FCD. We developed a prediction nomogram model of seizure outcome after resection surgery in patients with FCD that could help clinicians develop a personalized and risk-adapted therapeutic regimens for patients.

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AUTHORSHIP CONTRIBUTION

Study conception and design: YW

Data collection: YW, ZZ, LL

Analysis and interpretation of results: YW, ZZ, LL

Draft manuscript preparation: YW, ZZ, PL, LL, XZ

Critical revision of the article: PL, XZ

All authors (YW, ZZ, PL, LL, XZ) reviewed the results and approved the final version of the manuscript.

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