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Research Article

Association of Lateralized Interictal Epileptiform Discharges with Postsurgical Seizure Outcomes in Patients with Tuberous Sclerosis Complex: A 10-Year Retrospective Study at a Single Center

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Objective. Tuberous sclerosis complex (TSC) is a rare neurodevelopmental disorder often associated with intractable epilepsy, and surgical resection is the effective therapeutic approach to alleviate seizures in TSC patients. Scalp electroencephalogram (EEG) is a noninvasive method used to diagnose epilepsy; however, the relationship between scalp video-EEG findings and postsurgical seizure outcomes has not been fully evaluated in TSC patients. *Materials and Methods*. The relationship between clinical characteristics and seizure outcomes of TSC patients with 1-year, 5-year, and 10-year follow-ups was retrospectively analyzed. We explored the association of interictal epileptiform discharges (IEDs) with postsurgical seizure outcomes. Further, the differences in clinical characteristics among four IED patterns (focal, lateralized, multifocal, and generalized IEDs) were assessed. *Results*. A total of 82 patients were enrolled in this study. There were 82 patients with 1-year follow-up, 75 patients with 5-year follow-up, and 57 patients with 10-year follow-up, and the IEDs were associated with the postsurgical outcomes. Patients with focal, lateralized, and generalized IEDs had seizure freedom (SF) in 1-year follow-up, respectively. Intriguingly, patients with lateralized IEDs had long-term SF in 5-year and 10-year follow-ups. *Conclusions*. A significant association existed between IEDs and long-term postsurgical outcomes in TSC patients. TSC patients with lateralized IEDs often showed long-term SF and mild clinical epileptic characteristics. According to our study, IEDs may guide clinical care for TSC patients with intractable epilepsy.

1. Introduction

Tuberous sclerosis complex (TSC) is a rare neurodevelopmental disorder due to TSC1 or TSC2 gene variants, and approximately 80% of TSC patients have refractory seizures [1–3]. Our previous study showed that resective surgery improved the postsurgical outcomes, quality of life, and intelligence quotient (IQ) of TSC patients [4]. Interestingly, some clinical and imaging features have been reported to be potent predictors of postsurgical outcomes in patients with TSC [5–8]. It is meaningful to study the factors affecting the surgical outcomes of TSC patients.

Scalp electroencephalogram (EEG; including interictal and ictal scalp EEG) is a noninvasive and effective solution used to diagnose epilepsy, and the relationship between interictal epileptiform discharge (IED) findings and epileptic seizures has been the focus of clinical research [9–11]. Previous studies have reported that scalp EEG findings can predict seizure freedom following anterior temporal lobectomy, and temporal lobe surgery patients with unilateral IEDs had better surgical outcomes than those with bilateral IEDs [9, 12]. In addition, the low entropy of interictal gamma oscillations may be a useful biomarker for localizing the epileptogenic zone in patients with focal cortical dysplasia, and the automatic detection of IEDs has been used to evaluate the prognosis following adrenocorticotropic hormone (ACTH) therapy in patients with infantile spasms [13, 14]. However, the relationship between IEDs and long-term postoperative seizure outcomes in TSC patients is still unclear.

A few studies have shown that scalp EEG spikes predict impending epilepsy in TSC infants, and early IEDs in TSC infants predict epilepsy and neurodevelopmental outcomes [6, 8]. However, evidence regarding the effect of IEDs on long-term seizure outcomes is lacking. We collected data from 82 TSC patients with 1-year follow-up, 75 patients with 5-year follow-up, and 57 patients with 10-year follow-up to investigate the effect of IEDs on long-term postsurgical seizure outcomes. In addition, the differences in clinical characteristics among four different patterns of IEDs (focal, lateralized, multifocal, and generalized IEDs) were explored in TSC patients. This study is aimed at exploring the association of IEDs with long-term postsurgical seizure outcomes and clinical features in TSC patients.

2. Materials and Methods

2.1. Patients. We retrospectively reviewed TSC patients who underwent epilepsy surgery at Xinqiao Hospital from 2005 to 2021. The inclusion criteria were as follows: (1) patients diagnosed with TSC as defined by the diagnostic criteria from the 2012 International TSC Consensus Conference [15], (2) patients experienced intractable epilepsy and underwent epilepsy surgery at our comprehensive epilepsy center between 2005 and 2021, (3) patients with seizures occurring at least twice per month on average during the six months prior to surgery, and (4) patients who completed at least 1 year of follow-up. The exclusion criteria were as follows: (1) patients lost to follow-up, (2) patients without sufficient clinical information, including electrophysiological monitoring results and MRI images, and (3) patients with other neurological disorders. All procedures were performed according to the guidelines of the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from patients or guardians of patients in this study.

2.2. Preoperative Evaluations. The main preoperative evaluations included neurological physical examinations, genetic tests, computed tomography (CT), magnetic resonance imaging (MRI) [16],F-fluorodeoxyglucose (FDG) PET, scalp video-EEG recordings, stereoelectroencephalography (SEEG) monitoring, and IQ tests. Each scalp video-EEG recording included more than three habitual seizures, and SEEG was recorded in patients with multiple potential epileptogenic cortical tubers. According to our previous multicenter study, epileptogenic tubers were defined as follows: (i) a cortical tuber with focal ictal and interictal epileptiform discharges in the same brain region on scalp video-EEG with consistent seizure symptoms, (ii) an outstanding cortical tuber with focal ictal or interictal epileptiform discharges in the same brain region on scalp video-EEG with consistent seizure symptoms, or (iii) an outstanding cortical tuber with focal ictal and interictal epileptiform discharges in the same brain region on scalp video-EEG [4]. Outstanding cortical tubers described were defined as having a size $> 3 - 4$ cm and containing a nidus of calcification according to imaging results. Epileptogenic tubers showed hyperintense signs in T2-FLAIR images on MRI, hypometabolism in images on [16]F-FDG PET, and epileptiform discharges on EEG recordings. In this study, all tubers were counted based on the hyperintense signs in T2-FLAIR images on MRI, and the epileptogenic tubers were further identified combined with [16]F-FDG PET images and EEG recordings. The IQ scores were evaluated according to the Wechsler Adult Intelligence Scale IV (WAIS-IV) or Wechsler Children Intelligence Scale IV (Chinese Revision) (WAIS-IV or WISC-IV CR), and the baseline IQ scores were established 3 months prior to surgery.

2.3. Imaging Data Acquisition. MRI scans were performed in the Radiology Department of Xinqiao Hospital, and cortical tubers were identified on axial T2 fluid-attenuated inversion recovery (T2-FLAIR) MRI scans [16].F-FDG PET scans were performed using a Biograph 64 Truepoint PET/CT scanner and a Discovery ST system, and all procedures were performed in accordance with the guidelines issued by the Chinese Society of Nuclear Medicine. Attenuation correction was performed using CT. Cystic tubers, calcified tubers, subependymal nodules (SENs) and subependymal giant cell astrocytoma (SEGA) were defined based on CT and MRI scans. Two experienced neurosurgeons and neuroradiologists evaluated the imaging results and the electrophysiology findings independently and confirmed the identification of epileptogenic tubers in TSC patients with Cohen's kappa of 0.889 (95% CI 0.857-0.921).

2.4. Surgical Approach. Patients underwent resective surgery including lobectomy, tuberectomy, and tuberectomy plus. Lobectomy is the resection of partial or total brain lobe, tuberectomy is the resection of epileptogenic tuber only, and tuberectomy plus is the resection of epileptogenic tuber and 1–2 cm of perituberal cortex tissue. Lobectomy was applied in patients with multiple and/or large epileptogenic tubers in a brain lobe. Multiple lobectomies, multiple tuberectomies, and lobectomy combined with tuberectomy or tuberectomies plus were performed in patients with multiple epileptogenic tubers that could not be removed by lobectomy. There was no patient undergone more than one resective surgery.

2.5. Follow-Up. The patient recordings, follow-up recordings, and postoperative scalp video-EEG reports were systematically managed, and the postsurgical outcomes were assessed according to the International League Against Epilepsy (ILAE) criteria: ILAE type 1, seizure freedom; ILAE

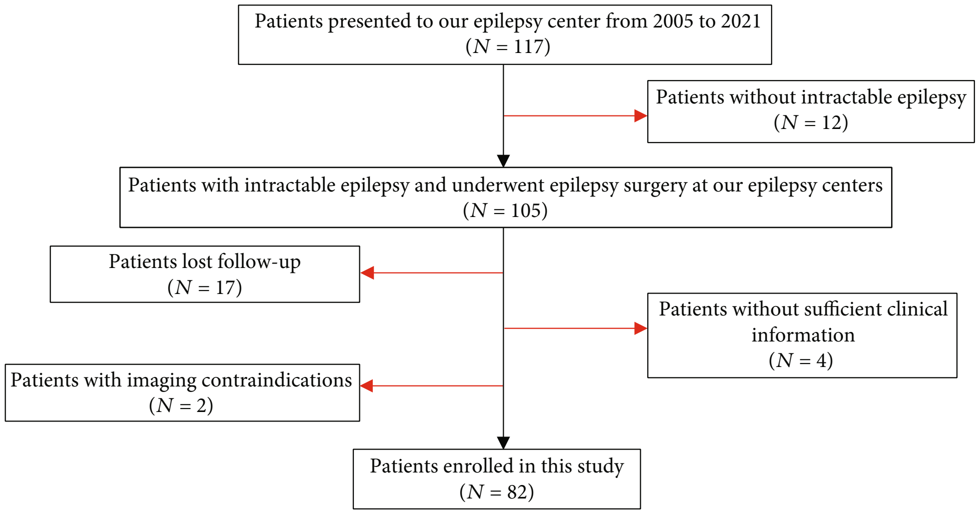

Figure 1: Flowchart of patient inclusion and exclusion criteria. A total of 117 TSC patients presented to our epilepsy center from 2005 to 2021, and 12 patients without intractable epilepsy, 17 patients losing to follow-up, 4 patients without sufficient clinical information, and 2 patients with imaging contraindications were excluded. In total, 82 patients were enrolled in this study.

type 2, focal aware seizures only, without other seizures; ILAE type 3, seizures on less than 4 days per year, with or without focal aware seizures; ILAE type 4, more than 50% reduction in the number of days affected by seizures with or without focal aware seizures; ILAE type 5, no significant change in seizures with up to 50% reduction ranging to 100% increase in days affected by seizures; and ILAE type 6, more than 100% increase in days affected by seizures [17]. According to the ILAE outcome classification, surgical outcomes were divided into seizure freedom (SF, ILAE type 1) and no-seizure freedom (No-SF, ILAE types 2–6) to assess the association between clinical characteristics and postsurgical outcomes in this study.

All patients completed at least a 1-year follow-up ($n = 82$). Additionally, patients who underwent epilepsy surgery between 2012 and 2016 completed a 5-year follow-up ($n = 75$), and those who underwent surgery between 2005 and 2011 completed a 10-year follow-up ($n = 57$). The completeness of epileptogenic tuber resection was assessed by two neurosurgeons and two neuroradiologists by comparing the preoperative and 6- to 12-month postoperative MRI scans with Cohen's kappa of 0.939 (95% CI 0.915-0.963).

2.6. Statistical Analysis. Simple descriptive statistics were used to evaluate the clinical information and quantitative tuber characteristics. Logistic regression analysis was used to assess the adjusted association between clinical characteristics and postsurgical outcomes (SF or No-SF). Stepwise regression (forward: LR) was performed with $\alpha = 0.05$ to eliminate multicollinearity, and collinearity diagnostics were monitored with variance inflation factors < 5.0 considered acceptable. Chi-square tests were performed for univariate analyses of categorical variables, and t tests were performed to compare continuous variables. The results are presented as the mean (range) or n (percentage). Significance was set at $P < 0.05$. Analysis was performed using the SPSS 23.0 package (version 23.0; SPSS, Inc., Chicago, IL).

3. Results

3.1. Clinical Information. A total of 117 TSC patients presented to our epilepsy center from 2005 to 2021, and 12 patients without intractable epilepsy, 17 patients losing to follow-up, 4 patients without sufficient clinical information, and 2 patients with imaging contraindications were excluded. In total, 82 patients (42 female and 40 male) were available for study inclusion (Figure 1).

The clinical characteristics of patients are reported in Table 1. The average IQ score was 57.4 (range: 30-93). 11 patients (13.4%) had TSC1 variants, 53 patients (64.6%) had TSC2 variants, and 18 patients (22.0%) had no variants detected. Among all patients, the mean age at seizure onset was 26.83 months (range: 1-216 months). The number of seizure types was 1.87 (range: 1-4), and epileptic spasms were present in the seizure type of 27 patients. There were 22 patients (26.8%) with 1 to 3 seizures per week, 30 patients (36.6%) with 4 to 10 seizures per week, and 30 patients (36.6%) with over 10 seizures per week. The mean number of antiseizure medications (ASMs) was 2.52 (range: 0-4) in TSC patient. Imaging (CT/MRI) revealed that 18 patients (22.0%) had cyst-like tubers, 27 patients (32.9%) had calcified tubers, 71 patients (86.6%) had SENs, and 25 patients (30.5%) had SEGA. 13 patients (15.9%) had 1 to 3 tubers, 54 patients (65.8%) had 4 to 6 tubers, and 15 patients (18.3%) had over 6 tubers in the brain. In total, 42 patients (51.2%) had one epileptogenic tuber, 29 patients (35.4%) had two epileptogenic tubers and 11 patients (13.4%) had three epileptogenic tubers. In addition, 67 patients (81.7%) underwent total resection of epileptogenic tubers, and 15 patients (18.3%) underwent partial resection of epileptogenic tubers.

Scalp video-EEG is a vital tool used to predict and diagnose epilepsy. Among the TSC patients in this study, 12 patients (14.6%) had focal IEDs, 31 patients (37.8%) had lateralized IEDs, 14 patients (17.1%) had multifocal IEDs,

Table 1: Clinical characteristics of TSC patients enrolled in the study.

Characteristics	Values
Sex	
Male	40 (48.8)
Female	42 (51.2)
IQ	57.4 (30-93)
Type of variant in TSC gene	
TSC1	11 (13.4)
TSC2	53 (64.6)
No variation	18 (22)
Age at onset (month)	26.83 (1-216)
Number of seizure types	1.87 (1-4)
Frequency of seizure	
1-3/w	22 (26.8)
4-10/w	30 (36.6)
>10/w	30 (36.6)
Number of ASMs	2.52 (0-4)
CT/MRI	
Cyst	18 (22.0)
Calcification	27 (32.9)
SEN	71 (86.6)
SEGA	25 (30.5)
Number of tubers	
1-3	13 (15.9)
4-6	54 (65.8)
>6	15 (18.3)
Number of epileptogenic tubers	
1	42 (51.2)
2	29 (35.4)
3	11 (13.4)
Total resection of epileptogenic tubers	
Yes	67 (81.7)
No	15 (18.3)
Interictal scalp video-EEG	
Focal	12 (14.6)
Lateralized	31 (37.8)
Multifocal	14 (17.1)
Generalized	25 (30.5)
Ictal scalp video-EEG	
Focal	19 (23.2)
Lateralized	33 (40.2)
Multifocal	17 (20.7)
Generalized	13 (15.9)
Surgery approach	
Single tuberectomy	13 (15.9)
Multiple tuberectomy	9 (11.0)
Lobectomy	6 (7.3)
Lobectomy+tuberectomy	54 (65.8)

Table 1: Continued.

Characteristics	Values
Postsurgical seizure outcomes	
1-year follow-up[a]	
SF	68 (82.9)
No-SF	14 (17.1)
5-year follow-up[b]	
SF	53 (70.7)
No-SF	22 (29.3)
10-year follow-up[c]	
SF	43 (75.4)
No-SF	14 (24.6)

Abbreviations: TSC: tuberous sclerosis complex; ASMs: antiseizure medications; SEN: subependymal nodules; SEGA: subependymal giant cell astrocytoma; SF: seizure freedom. Values are n (%) or mean (range). [a]Available patient data $n = 82$. [b]Available patient data $n = 75$. [c]Available patient data $n = 57$.

and 25 patients (30.5%) had generalized IEDs. Hypsarrhythmia was present in the IEDs of 16 patients. Ictal scalp video-EEG showed these four patterns in 19 (23.2%), 33 (40.2%), 17 (20.7%), and 13 (15.9%) TSC patients. The surgical treatments consisted of single tuberectomy in 13 patients (15.9%), multiple tuberectomy in 9 patients (11.0%), lobectomy in 6 patients (7.3%), and tuberectomy plus lobectomy in 54 patients (65.8%). Tuberectomy plus lobectomy was the most used surgical treatment in TSC patients. Furthermore, we evaluated the postsurgical seizure outcomes of the TSC patients at the 1-year ($n = 82$), 5-year ($n = 75$), and 10-year ($n = 57$) follow-ups.

3.2. Association between IED Findings and Postsurgical Seizure Outcomes. The relationship between clinical characteristics and postsurgical seizure outcomes was explored in TSC patients (Table 2). The interictal scalp video-EEG ($P < 0.01$), number of ASMs ($P < 0.05$), and number of tubers ($P < 0.05$) were associated with seizure outcomes in TSC patients with 1-year follow-up. The interictal scalp video-EEG ($P < 0.01$) and number of epileptogenic tubers ($P < 0.05$) were associated with surgical outcomes in TSC patients with 5-year and 10-year follow-ups.

There were four patterns of IEDs: focal IEDs (unique unilateral focal IEDs with or without generalized IEDs, Figure 2(a)), lateralized IEDs (or unilateral hemisphere IEDs with or without generalized IEDs, Figure 2(b)), multifocal IEDs (two or more independent focal IEDs with or without generalized IEDs, Figure 2(c)), and generalized IEDs (any bilaterally synchronous and symmetric pattern IEDs without focal IEDs, but it can be in a restricted field, Figure 2(d)). To patients with multiple variability of IEDs, two observers reviewed all the EEGs, determined the dominant pattern, and reached final consistency of IED patterns. And EEG abnormalities involving a larger area prompt a larger resection. We explored the association between the four IED patterns and postsurgical seizure outcomes in TSC patients with 1-year, 5-year, and 10-year follow-ups (Table 3). Results showed that focal, lateralized, and generalized IEDs were

Table 2: The relationship between clinical characteristics and surgical outcome in TSC patients.

Follow-up time	Demographic characteristics	β	SE	Wald	P value	Exp (β)	95% CI	
1-year follow-up	Interictal scalp EEG	1.584	0.487	10.591	0.001**	4.876	1.878	12.661
	Number of ASMs	1.659	0.653	6.455	0.011*	5.253	1.461	18.891
	Number of tubers	2.241	0.934	5.762	0.016*	9.407	1.509	58.651
5-year follow-up	Interictal scalp EEG	1.335	0.378	12.447	0.000**	3.799	1.810	7.973
	Number of epileptogenic tubers	0.789	0.387	4.151	0.042*	2.202	1.030	4.706
10-year follow-up	Interictal scalp EEG	1.988	0.627	10.046	0.002**	7.300	2.135	24.958
	Number of epileptogenic tubers	1.460	0.589	6.139	0.013*	4.308	1.357	13.678

Abbreviations: TSC: tuberous sclerosis complex; ASMs: antiseizure medications. $^{**}P < 0.01$ and $^{*}P < 0.05$.

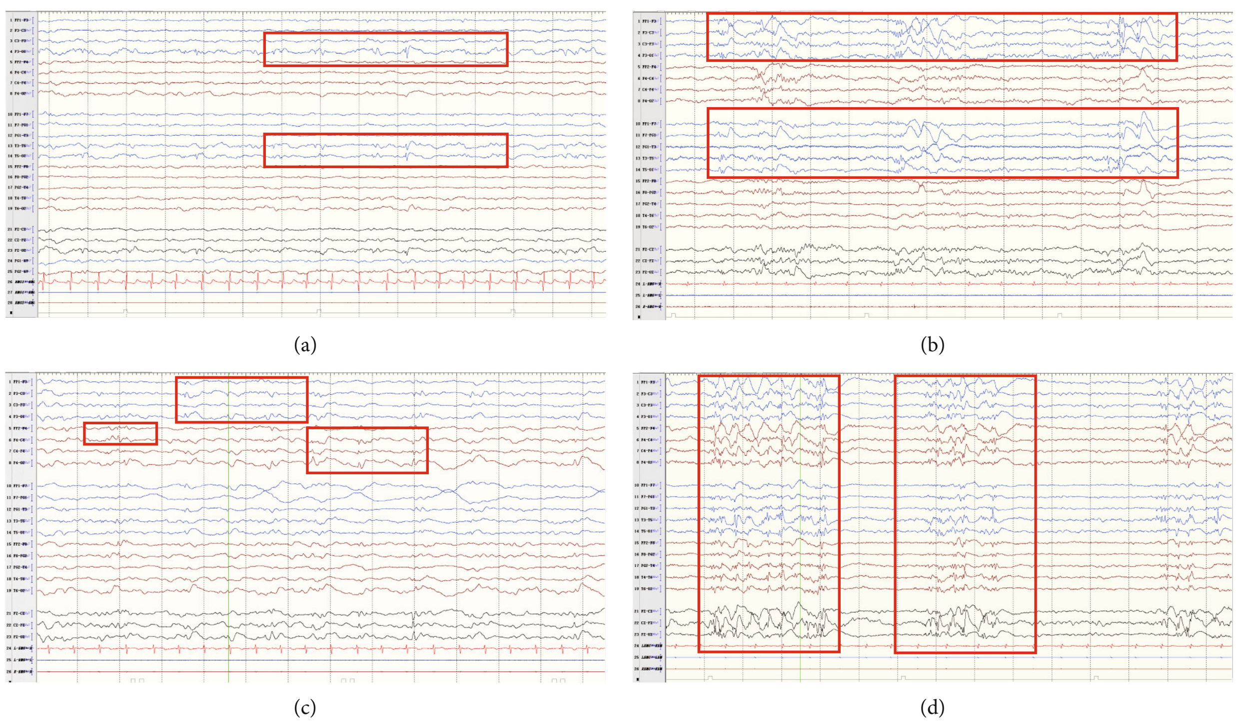

Figure 2: Four patterns of interictal epileptiform discharges (IEDs). (a) Focal IEDs. (b) Lateralized IEDs. (c) Multifocal IEDs. (d) Generalized IEDs.

Table 3: The relationship between IED patterns and postsurgical seizure outcomes in TSC patients.

IED patterns	1-year follow-up ($n = 82$)		5-year follow-up ($n = 75$)		10-year follow-up ($n = 57$)	
	SF ($n = 60$)	No-SF ($n = 22$)	SF ($n = 53$)	No-SF ($n = 22$)	SF ($n = 40$)	No-SF ($n = 17$)
Focal	10 (83.3)*	2 (16.7)	9 (75)	3 (25)	8 (72.7)	3 (27.3)
Lateralized	28 (90.3)**	3 (9.7)	22 (75.9)**	7 (24.1)	15 (78.9)*	4 (21.1)
Multifocal	10 (71.4)	4 (28.6)	9 (64.3)	5 (35.7)	8 (66.7)	4 (33.3)
Generalized	18 (72)*	7 (28)	10 (50)	10 (50)	9 (60)	6 (40)

Abbreviations: IEDs: interictal epileptiform discharges; SF: seizure freedom. Values are n (%). $^{**}P < 0.01$ and $^{*}P < 0.05$.

associated with postsurgical SF in TSC patients with 1-year follow-up. Intriguingly, lateralized IEDs were also associated with SF in TSC patients with 5-year and 10-year follow-ups. These results showed that TSC patients with lateralized IEDs were more likely to had long-term SF than patients with focal, multifocal, and generalized IEDs.

3.3. Association between IED Patterns and Clinical Characteristics. The relationship between interictal IEDs and clinical characteristics was evaluated in TSC patients (Tables 4 and 5). The seizure frequency in patients with focal ($P < 0.05$) and lateralized ($P < 0.01$) IEDs was lower than that in patients with generalized IEDs, and patients with

Table 4: The relationship between IED patterns and clinical characteristics in TSC patients.

IED patterns	Gene variant		Seizure frequency			Number of ASMs				IQ
	TSC1	TSC2	1-3/w	4-10/w	>10/w	1	2	3	4	
Focal	2 (22.2)	7 (77.8)	6 (50)	3 (25)	3 (25)[a]	2 (16.7)	4 (33.3)	4 (33.3)	2 (16.7)	59.6 (35-71)
Lateralized	4 (17.4)	19 (82.6)	12 (38.7)	15 (48.4)	4 (12.9)[b,c]	5 (16.1)	14 (45.2)	9 (29.0)	3 (9.7)	57.1 (39-93)
Multifocal	2 (16.7)	10 (83.3)	2 (14.3)	5 (35.7)	7 (50)	2 (14.3)	5 (35.7)	4 (28.6)	3 (21.4)	56.9 (31-42)
Generalized	3 (15)	17 (85)	2 (8)	7 (28)	16 (64)	1 (4)	10 (40)	8 (32)	6 (24)	57.1 (30-86)

Abbreviations: IEDs: interictal epileptiform discharges; TSC: tuberous sclerosis complex; ASMs: antiseizure medications. Values are *n* (%) or mean (range). [a]$P < 0.05$, the percentage of seizure frequency in patients with this group versus the data in the generalized group. [b]$P < 0.01$, the percentage of seizure frequency in patients with this group versus the data in the multifocal group. [c]$P < 0.01$, the percentage of seizure frequency in patients with this group versus the data in the generalized group.

Table 5: The relationship between IED patterns and number of tubers in TSC patients.

IED patterns	Number of tubers	Number of epileptogenic tubers	Ratio of epileptogenic tubers
Focal	4.22 (1-7)	1.56 (1-2)	0.37 (0.25-1)
Lateralized	5.03 (2-8)	1.61 (1-3)[a]	0.32 (0.20-0.67)
Multifocal	5.29 (2-8)	1.93 (1-4)	0.36 (0.14-0.67)
Generalized	5.11 (2-9)	2.11 (1-4)	0.41 (0.20-0.67)

Abbreviations: IEDs: interictal epileptiform discharges; TSC: tuberous sclerosis complex. Values are mean (range). [a]$P < 0.05$, the number of epitubers in the focal group versus the data in the generalized group.

lateralized IEDs showed a lower seizure frequency than patients with multifocal IEDs ($P < 0.01$; Table 4). In addition, patients with lateralized IEDs had fewer epileptogenic tubers than patients with generalized IEDs ($P < 0.05$; Table 5). There was no association of the IED patterns with gene variant, number of ASMs, IQ, number of tubers, and ratio of epileptogenic tubers in TSC patients.

Neuroimaging is a vital tool used to facilitate the detection of structural epileptogenic lesions and widely used to diagnose epileptogenic tubers in TSC patients. The common imaging types of epileptogenic tubers in TSC patients include cyst-like tubers (Figure 3(a)), calcified tubers (Figure 3(b)), SEN (Figure 3(c)), and SEGA (Figure 3(d)). We further assessed the association between IED patterns and imaging features of tubers in TSC patients (Table 6), and results showed that patients with lateralized IEDs had fewer calcified tubers than patients with generalized IEDs ($P < 0.01$).

4. Discussion

Few studies explored the prognostic implications of IEDs in patients with TSC. In this study, we evaluated the association of postsurgical seizure outcomes with clinical characteristics in TSC patients and found that interictal scalp video-EEG findings were an effective predictor of long-term postsurgical seizure outcomes. Furthermore, this single-center study focused on the association of IEDs with postsurgical seizure outcomes and clinical characteristics in TSC patients. Ictal scalp video-EEG and intracranial video-EEG can be used to localize the epileptic foci and predict the prognosis of resective epilepsy surgery, and interictal EEG is usually used to define the irritation zone [16, 18–20]. Previous study highlighted the value of scalp video-EEG, particularly interictal EEG, in predicting the surgical outcome of epilepsy patients, and the present study supported this conclusion [12, 21, 22]. Our study showed that IEDs were associated with postsurgical seizure outcomes, and patients with lateralized IEDs had better surgical effects at the 10-year follow-up than patients with focal, multifocal, and generalized epileptic discharges. These results provide novel insight into the clinical application and potent value of IEDs.

Focal epileptic discharges are the most limited epileptic scalp video-EEG patterns and associated with the mildest symptoms among all types of scalp video-EEG [23]. However, studies had shown that patients with focal epileptic discharges did not always experience SF after resection of the actual seizure-onset zone, and some cases showed that areas adjacent to the seizure-onset zone could also trigger epileptic seizures [20, 24]. Perituberal cortical hyperexcitability were also found in patients and rats with TSC, and evidence from intracranial EEG, PET, magnetoencephalography (MEG), and histologic and immunohistochemical labeling showed that the perituberal cortex presented similar pathological, histologic, immunohistochemical, and molecular features with tubers and could be the source of epileptiform discharges and seizure onset [25–29]. In addition, increasing evidence supported that the perituberal areas should be removed in order to achieve seizure freedom [25, 29], and updated European expert clinical recommendations for the management of epilepsy in patients with TSC suggested that resection beyond tuber margins was associated with greater probability of seizure freedom [3]. Major et al. reported three pediatric patients who underwent intracranial electrocorticography (ECoG) prior to tuber resection, and the tuber was electrographically silent, whereas the adjacent cortex exhibited high-frequency epileptiform discharges. The patients experienced a drastic reduction in seizure frequency when the tubers and electrically active adjacent cortex were resected [30]. Those results showed that epileptogenicity of cortical tubers may derive not from the lesion itself, but rather from the perturbation or abnormal

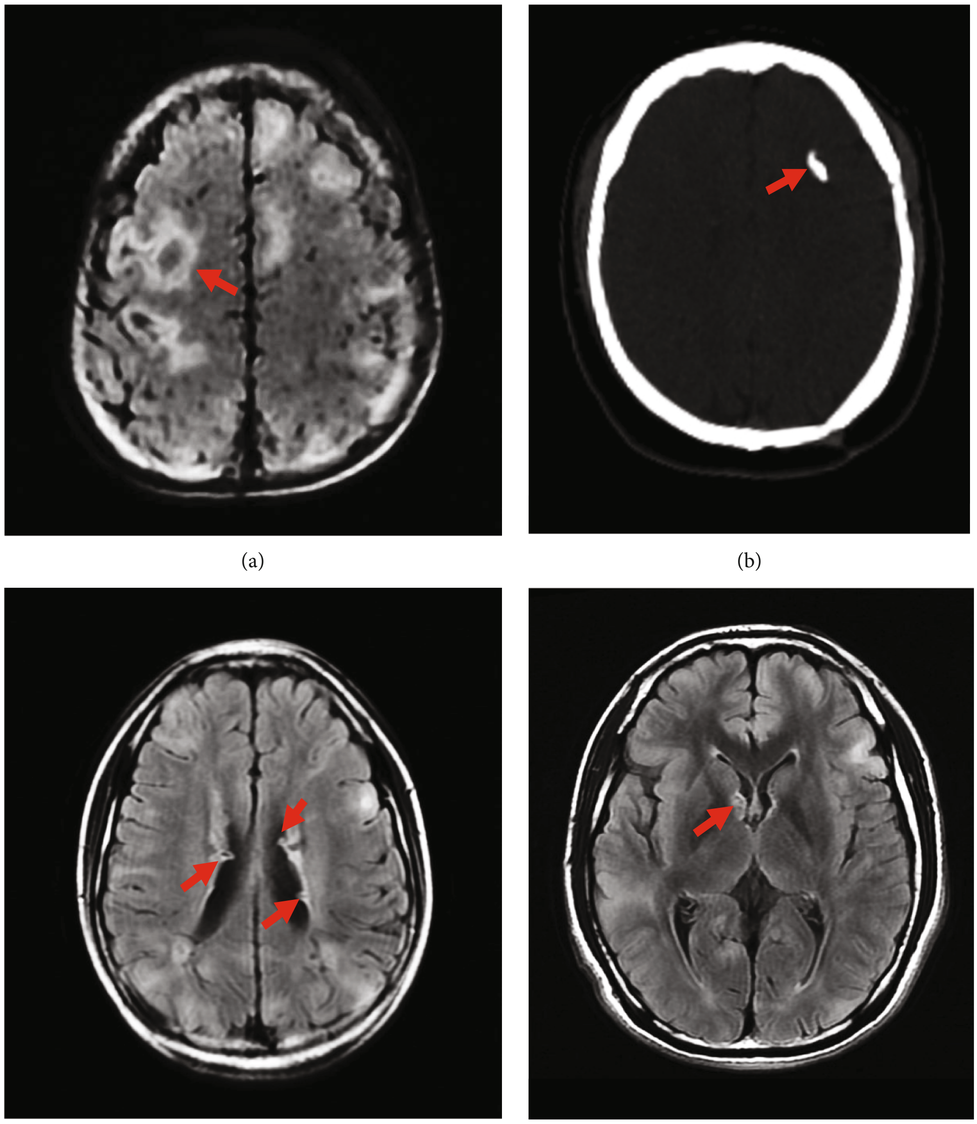

Figure 3: Typical imaging features of tubers in TSC patients. (a) Cyst-like tubers. (b) Calcified tubers. (c) SEN. (d) SEGA. The tubers were shown by the red arrows.

Table 6: The relationship between IED patterns and imaging features in TSC patients.

IED patterns	Cyst		Calcification		SEN		SEGN	
	Yes	No	Yes	No	Yes	No	Yes	No
Focal	3 (25)	9 (75)	3 (25)	9 (75)	11 (91.7)	1 (8.3)	4 (33.3)	8 (66.7)
Lateralized	5 (16.1)	26 (83.9)	6 (20.7)[a]	25 (79.3)	27 (87.1)	4 (12.9)	10 (32.2)	21 (67.7)
Multifocal	3 (21.4)	11 (78.6)	4 (28.6)	10 (71.4)	12 (85.7)	2 (14.3)	4 (28.6)	10 (71.4)
Generalized	7 (28)	18 (72)	14 (56)	11 (44)	21 (84)	4 (16)	7 (28)	18 (72)

Abbreviations: IEDs: interictal epileptiform discharges; TSC: tuberous sclerosis complex; SEN: subependymal nodules. Values are n (%). [a]$P < 0.01$, the percentage of patients with calcified tubers versus the data in the generalized group.

development of the surrounding cortex. Lateralized epileptic discharges are a special form of focal IEDs, and a wider range of tissue, including epileptogenic tubers and perituberal cortex, was resected in patients with lateralized IEDs than focal IEDs. Our study revealed that patients with lateralized IEDs had a longer time of postoperative seizure freedom than patients with focal IEDs and supported resection of epileptogenic tubers and perituberal cortex had greater superiority in TSC patients. These results provided a new guidance for resective epilepsy surgery in TSC patients.

In recent studies, epileptogenesis and surgical outcomes have often been assessed by the seizure-onset pattern captured through intracranial recording (depth electrodes or a subdural grid) [31, 32]. However, the practical application of intracranial recording is difficult before surgery. Therefore, it is necessary to understand the connection between scalp video-EEG findings and clinical characteristics. We analyzed the relationship between interictal scalp video-EEG features and clinical characteristics in TSC patients and found that patients with focal and lateralized IEDs showed lower seizure frequency and epileptogenic tuber counts than patients with generalized IEDs. In addition, imaging results are vital for the diagnosis of epileptogenic tubers in TSC patients [33, 34], and calcification, cystic change, SENs, and SEGA are risk factors that are useful for identifying epileptogenic tubers [35, 36]. Our previous study reported that tuber with calcified feature on MRI/CT was a key factor influencing postoperative seizure freedom and should be considered good indicator for epilepsy surgery in patients with TSC [4]. In this study, we analyzed the association between interictal IED patterns and imaging features in TSC patients, and fewer calcified tubers were observed in patients with lateralized IEDs than generalized IEDs. These results supported that patient with lateralized IEDs had long-term SF.

This study has some limitations. First, the sample of enrolled patients was smaller than desired because this study was a single-center study and the incidence of TSC-related epilepsy is low. Second, not all patients had complete information on clinical characteristics because of the retrospective and uncontrolled design of the study. Third, all enrolled patients underwent surgery, and patients with preoperative predictors of poor surgical outcomes were excluded before surgery; therefore, the surgical outcomes of the enrolled patients could be biased to some extent.

5. Conclusions

In conclusion, this study indicates that IEDs were associated with postsurgical outcomes in TSC patients and lateralized IEDs was associated with long-term postsurgical SF and mild clinical features of epilepsy. Therefore, lateralized IEDs can be used as an effective biomarker to assess the prognosis of TSC patients following epilepsy surgery. We believe that this study will provide important implications for the clinical care of TSC patients.

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authors' Contributions

ZKW and SYL designed this study. SJL and ZKW contributed to collecting clinical data and writing the manuscript. SYL, HY, CQZ, ZHL, SQL, and MW performed the surgery and study supervision. ZH, YL, KXH, XLY, WW, and JYZ followed up all patients enrolled in this study. SJL, ZKW, SFW, and SX finished the statistical analysis. XJS and LHL recorded and analyzed scalp EEG results. ZKW and SYL reviewed the final manuscript and provided comments. All authors read and approved the final manuscript.

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