Assessing Risk for Relapse among Children with Infantile Spasms Using the Based Score after ACTH Treatment: A Retrospective Study

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ABSTRACT

Introduction: Even though adrenocorticotropic hormone (ACTH) demonstrated powerful efficacy in the initially successful treatment of infantile spasms (IS), nearly one-half of patients whose spasms were once suppressed experienced relapse. There is currently no validated method for the prediction of the risk of relapse. The Burden of Amplitudes and Epileptiform Discharges (BASED) score is an electroencephalogram (EEG) grading scale for children with infantile spasms. We sought to determine whether an association exists between the BASED score after ACTH treatment and relapse after initial response with ACTH.

Methods: Children with IS who achieved initial response after ACTH treatment were selected as the study subjects. Those who experienced relapse within 12 months after ACTH treatment were categorized as the relapse group, and those who did not were categorized as the non-relapse group. Their general clinical data and EEG data

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(using BASED scoring) after ACTH treatment were collected, and compared between groups. Cox proportional hazards models were fit to determine factors associated with relapse.

Results: A total of 64 children with IS were enrolled in the study, of which 37 (57.8%) experienced a relapse, and the median duration after ACTH treatment was 3 (1.5, 6) months. The BASED score was significantly higher in the relapse group than in the non-relapse group. Cox modeling demonstrated that BASED score was independently associated with relapse. The patients with a score greater than or equal to 3 showed a high rate (89.3%) of relapse. The relapse group had stronger, more stable EEG functional networks than the non-relapse group, and there were obvious correlations between BASED score and functional connectivity.

Conclusion: This study suggests the BASED score after ACTH treatment has potential value as a predictor for relapse after initial response. Children with IS who have a BASED score greater than or equal to 3 after the initial response of ACTH carry a high risk of relapse within 1 year.

Keywords: Infantile spasms; Relapse; Risk factors; BASED score; Adrenocorticotropic hormone; Dynamic functional connectivity

Key Summary Points

Relapse occurs in nearly half of the children of infantile spasms, and there is no effective way to predict it.

Our study attempted to use the Burden of Amplitudes and Epileptiform Discharges (BASED) score to assess the risk of relapse.

Our study suggests that those patients with infantile spasms who have a BASED score greater than or equal to 3 seem to have a higher risk of relapse.

Ideally, the BASED score after treatment is reduced to lower than 2.

INTRODUCTION

Infantile spasm (IS) is a rare early infantile epileptic encephalopathy characterized by epileptic spasms with or without hypsarrhythmia, and with poor prognosis [1]. Prompt cessation of the spasms and resolution of hypsarrhythmia on electroencephalogram (EEG) were thought to be associated with a favorable cognitive outcome [2, 3], as important as the long-term remission of spasms [4]. Adrenocorticotropic hormone (ACTH) is currently the preferred first-line treatment for infantile spasms, but because of the side effects of ACTH therapy, including hypertension, hypokalemia, metabolic alkalosis, irritability, brain atrophy, and serious infection, it cannot be used long term [5]. The short-term response rate of ACTH therapy was 42–87%, but relapse still occurred in nearly half of the children studied [6]. Dressler et al. [7] revealed that the relapse rate was 56% in those patients who responded after receiving ACTH therapy.

EEG is the main diagnostic technique for the precise classification of epileptic seizures and syndromes, and broadly used in studies on epilepsy. For example, the early response and prognosis of infantile spasms can be predicted by analyzing the multiscale entropy or high-frequency oscillations of EEG [8–11]. The Burden of Amplitudes and Epileptiform Discharges (BASED) score developed by Mytinger et al. [12] is a reliable interictal EEG grading scale for children with infantile spasms. It can help determine the presence or absence of epileptic encephalopathy in the setting of infantile spasms in pretreatment and posttreatment studies. In this convenient and rapid method, clinical electrophysiologists assign a score by examining the EEG recordings with the naked eye without the need for external statistical or analytical tools [12].

Previous studies have concentrated on the short-term response and long-term outcome of ACTH treatment of IS. Despite relapse after ACTH therapy being such an important issue, the factors related to relapse and its prevention have not yet been fully investigated. In this retrospective cohort study, the BASED scale was

used to determine whether there was a difference between children with IS who had relapsed and those who had not after short-term response with ACTH treatment. Moreover, the differences and similarities of the groups in brain functional connectivity networks were also explored.

METHODS

Study Subjects

Children with IS who had a short-term response by ACTH treatment and were reexamined in the Department of Pediatrics, Chinese PLA General Hospital, from 2008 to 2021 were recruited as the research subjects. To avoid miscategorization due to spasms not readily recognized visually, all subjects who were not known to have experienced relapse were reexamined by video EEG in the ward of the hospital. Patients who experienced relapse within 12 months after ACTH treatment were categorized as the relapse group, and those who did not were categorized as the non-relapse group.

Inclusion criteria were as follows: (i) IS [1] was diagnosed on the basis of EEG results and clinical characteristics, as confirmed by two pediatric neurologists; (ii) patients completed 14 days of ACTH treatment and achieved complete cessation of seizures at the end of the treatment; (iii) EEG double-check was performed within the last 2 days before the end of ACTH treatment.

Exclusion criteria were as follows: (i) anti-seizure medicines (ASMs) were adjusted during ACTH treatment, before relapse or last follow-up; (ii) frequency of spasms before treatment was less than one time per day; (iii) severe artifact on EEG; (iv) absence of clinical or EEG data; (v) the follow-up time of the non-relapse group was less than 1 year; (vi) there were obvious relapse causes such as severe infection or trauma.

ACTH Treatment

After admission, all patients with IS were treated with vitamin B6 (100 mg/day) for 3 days to exclude pyridoxine-dependent epilepsy, and subsequently, ACTH (2.5 U/kg/day, $\leq$ 25 U/day) was intravenously administered for 14 days [13, 14].

EEG Recording

EEG was recorded using the standard international 10/20 system, with 19 electrodes at a sampling frequency of 256 Hz. At least 2 h of video-EEG monitoring, including a slow-wave sleeping period, was recorded [9]. The EEG data were analyzed with a bipolar montage.

BASED Scoring

Two experienced neuroelectrophysiologists independently scored the EEGs following the 2021 BASED scoring criteria [12]. When EEG scoring was discrepant, a senior neuroelectrophysiologist served as a tiebreaker. All the investigators were blinded to the previous reports of EEG and clinical outcomes. The EEG data were reviewed using the Micromed EEG system (Zerman di Mogliano Veneto, Italy) and analyzed with a bipolar montage.

Clinical Data

Clinical data including IS etiology, the presence or absence of pathogenic structural abnormalities on MRI (such as focal cortical dysplasias, gliosis caused by post-encephalitis, hypoxic–ischemic encephalopathy, neonatal hypoglycemia, etc.) [6, 15–17], age of spasm onset, time from onset to receive ACTH treatment, the dosage of ACTH, the presence or absence of hypsarrhythmia (both typical and atypical hypsarrhythmia) [1, 18, 19] before and after ACTH treatment, exposure of ASMs, oral glucocorticoid therapy, and the frequency of spasms (mean of 1 week before ACTH treatment) were recorded.

Grouping by Treatment Response and Relapse

Short-term response of ACTH treatment was defined as no witnessed spasms at the end of ACTH therapy and subsequent 4 weeks [14]. Relapse was confirmed at any stage after short-term response as follows: (i) any episode of spasms occurring in clusters; (ii) two or more episodes of spasms that occur solely but not in clusters; and (iii) subtle spasms (if accompanied by an EEG showing appropriate changes) [1]. Patients experiencing a relapse within 1 year after the short-term response were categorized as the relapse group, and those who did not were categorized as the non-relapse group. Each group was divided into two subgroups according to etiology (definitive versus unknown).

EEG-Based Functional Connectivity States Assessment

EEG signals in the duration by BASED scoring were selected to measure the functional connectivity. To avoid bias, the subjects with BASED score ≥ 2 were selected (epileptiform discharges could be identified to choose the duration of 5 min for BASED scoring), and propensity score matching (PSM) was used to eliminate the bias of other factors.

All the data analyses of selected EEG signals were performed with Python (Python Software Foundation, https://www.python.org/). First, the power line noise (50 Hz) was notch-filtered, and channels of midline were excluded from analysis (three channels in all datasets). Then, a bandpass filter (fourth-order Butterworth, 14–40 Hz) was applied to all data before analysis.

To capture the time-varying epileptiform discharges of the brain in the interictal period, the filtered signals were divided into a series of short-time segments by the sliding-window-based approach, representing a series of windowed functional connectivity matrices along the BASED scoring period. The window size was set to 3 s, and the step size was set to 1 s. After that, we calculated the coherence value of two channels each to obtain the paired coherence matrix in every short time window. These matrices are squared matrices whose dimension is equal to the number of channels. Briefly, coherence value can measure locally phase-locked behavior between two time series in both frequency and time domains. As a result, the 5-min measurement duration was segmented into a series of windowed functional connectivity (FC) matrices for each subject.

To assess the reoccurring functional connectivity patterns (states) during the BASED scoring duration, we applied *k*-means clustering, an unsupervised learning method, on the concatenated windowed FC matrices across the entire group, to identify various clusters representing distinct FC states. We determined the optimal number of clusters is five ($k = 5$), based on the silhouette criterion of cluster validity index. Further, we investigated the proportion of FC states by computing the percentage of total windows belonging to one state.

Ethics Statement

This study was approved by the ethics committee of First Medical Center of PLA General Hospital (S2021-569-01). This study was a retrospective cohort study, patient identity remained anonymous, and the requirement for informed consent was waived by the ethics committee of First Medical Center of PLA General Hospital owing to the observational nature of the study (S2021-569-01).

Statistical Analysis

SPSS 26.0 statistical software and R statistical programming language version 4.1.2 (R Programming) were used for analysis. Clinical data description was demonstrated in the form of mean and standard deviation for the normally distributed variables or median and interquartile range for the non-normally distributed variables. Independent two-sample *t*-test, chi-squared test, Fisher's exact test, or rank-sum test was implemented for analyzing the above observation indicators. Logistic regression model and Cox proportional hazards regression model were utilized to identify the risk factors

of relapse. For both models, univariate regression analysis was performed. Then, the factors with a *p*-value of less than 0.2 were selected for multivariate analyses. Analysis of variance (ANOVA), chi-squared test, and independent two-sample *t*-test were performed to compare the properties of functional connectivity (FC) states between the groups. Spearman correlation coefficient was computed for the FC states and the BASED score. A *p*-value of less than 0.05 is considered statistically significant.

RESULTS

A total of 103 children with IS who had a short-term response with ACTH treatment and returned for follow-up were screened. Among them, 8 non-relapse patients had a follow-up of less than 1 year, 3 children experienced a relapse at the duration of serious infection, and the ASMs of 28 patients were adjusted during follow-up. The 39 patients above were excluded. Finally, a total of 64 children were enrolled in the study (Fig. S1). Among them, 37 children (57.8%) experienced relapse, and the median duration after ACTH treatment was 3 (1.5, 6) months; the other 27 children (42.2%) remained seizure free in the 30 (16, 40) months of follow-up.

There was a statistically significant difference in the BASED score of EEG after ACTH treatment between the two groups ($p < 0.001$), but no significant group differences emerged for the other factors (including etiology, presence, or absence of pathogenic structural abnormalities on MRI, age of spasm onset, time from onset to receive ACTH treatment, the dosage of ACTH, the presence or absence of hypsarrhythmia before and after ACTH treatment, respectively, etc.) (Table 1).

In both the relapse group and the non-relapse group, no significant group difference emerged for the BASED score of EEG after ACTH treatment between the two subgroups (definitive etiology versus unknown etiology). Similar results were observed overall in the 64 patients; there was no significant difference in the BASED score of EEG after ACTH treatment between

those patients who had definitive etiology and those with unknown etiology (Table 2).

The results of univariate logistic regression analysis showed that the independent risk factor for relapse was BASED score [$p < 0.001$, odds ratio (OR) 2.26, 95% confidence interval (CI) 1.54–3.62] (Table 3). Determinants with $p \leq 0.20$ in the univariate logistic regression models (presence of hypsarrhythmia after ACTH, definitive or unknown etiology, VPA exposure history, the interval from onset to receive ACTH treatment, presence of hypsarrhythmia before ACTH treatment, BASED score) were included in the multivariate model; the results were consistent with the univariate logistic regression, showing that an elevated BASED score may correlate with a higher risk of relapse ($p = 0.001$, OR 2.23, 95% CI 1.43–3.83; Table 3).

The results of univariate Cox regression analysis showed that the independent risk factors for relapse were BASED score [$p < 0.001$, hazard ratio (HR) 1.56, 95% CI 1.28–1.89], VPA exposure history ($p = 0.041$, HR 1.97, 95% CI 1.03–3.77) and presence of hypsarrhythmia after ACTH treatment ($p = 0.011$, HR: 3.18, 95% CI 1.31–7.71; Table 4). Determinants with $p \leq 0.20$ in the univariate logistic regression models (presence of hypsarrhythmia after ACTH, definitive or unknown etiology, VPA exposure history, interval from onset to receive ACTH treatment, presence of hypsarrhythmia before ACTH treatment, number of ASMs, BASED score) were included in the multivariate model, indicating that an elevated BASED score may correlate with a higher risk of relapse ($p < 0.001$, HR 1.5, 95% CI 1.2–1.9; Table 4, Fig. S2), which was consistent with the multivariate logistic regression. The same result was observed in the cohort of 72 cases (including the 8 patients with non-relapse who were followed up for less than 1 year) (Table S1, Fig. S3).

The BASED score after ACTH treatment has good clinical value ($p < 0.001$, AUC: 0.82, 95% CI 0.713–0.925; Fig. 1) for predicting relapse. The optimal cutoff value of the BASED score was 3 (sensitivity 0.893, specificity 0.667, Youden's index 0.56). There were 27 (42.2%) patients who were free of seizure more than 12 months after the short-term response (Fig. 2a). In total, 89.3% of patients with a

Table 1 Comparison of clinical data between relapse and non-relapse groups

	Relapse group ($n = 37$)	Non-relapse group ($n = 27$)	Test statistics	p-Value
Gender (male/female)	25/12	15/12	0.961	0.434[a]
Presence of hypsarrhythmia before ACTH treatment	28	24	1.789	0.213[a]
Pathogenic structural abnormalities on MRI	8	6	0.003	1[a]
Definitive etiology	20	10	1.815	0.211[a]
Number of ASMs				0.594[b]
1	18	16		
2	13	9		
3	6	2		
VPA exposure history	20	8	3.784	0.075[a]
TPM exposure history	33	24		1.000[b]
VGB exposure history	1	2		0.568[b]
Hormonal therapy history	5	3		1.000[b]
Presence of hypsarrhythmia after ACTH treatment (months)	6	1		0.223[b]
Interval from onset to receive ACTH treatment (months)	2 (1, 5)	1.5 (0.75, 3)	− 1.576	0.116[c]
Age at spasm onset (months)	6 (4, 7.5)	6 (4, 7)	− 0.475	0.640[c]
Frequency of spasms (count per day)	25 (13, 75)	45 (15, 95)	− 1.176	0.243[c]
Dosage of ACTH (IU/kg)	2.7 ± 0.43	2.77 ± 0.43	− 0.61	0.544[d]
BASED score				**< 0.001**[b]
0	2	9		
1	6	8		
2	4	7		
3	7	1		
4	9	1		
5	9	1		

ACTH adrenocorticotropic hormone, *ASM* antiseizure medication, *BASED* Burden of Amplitudes and Epileptiform Discharges, *TPM* topiramate, *VGB* vigabatrin, *VPA* valproate

A bold p-value indicates statistical significance; data are expressed as number, mean ± standard deviation, or median (range)

[a]Chi-squared test

[b]Fisher's exact test (test statistic is identical with p-value)

[c]Rank-sum test

[d]Independent two-sample t-test

Table 2 Comparison of BASED score between subgroups according to etiology

	Definitive etiology	Unknown etiology	Test statistics	p-Value
Relapse group (n = 37)	20	17		
BASED score				0.165[a]
0	1	1		
1	1	5		
2	4	0		
3	4	3		
4	4	5		
5	6	3		
Non-relapse group (n = 27)	10	17		
BASED score				0.512[a]
0	4	5		
1	2	6		
2	2	5		
3	0	1		
4	1	0		
5	1	0		
Study cohort (n = 64)	30	34		
BASED score				0.307[b]
0	5	6		
1	3	11		
2	6	5		
3	4	4		
4	5	5		
5	7	3		

BASED Burden of Amplitudes and Epileptiform Discharges
[a]Chi-squared test
[b]Fisher's exact test (test statistic is identical with p-value)

BASED score less than or equal to 3 experienced a relapse within 12 months after short-term response, but 33.3% of those patients had a BASED score less than or equal to 2 ($p = 0.001$, Fig. 2b). Similar results were observed in the 72-case cohort (Figs. S4, S5).

After PSM (factors like presence of hypsarrhythmia after ACTH treatment, VPA exposure history, and interval from onset to receive ACTH; ratio is 1:2), 24 patients with a BASED score $\geq$ 2 were selected for functional connectivity assessment, where 8 non-relapse and 16 relapses were assigned to the corresponding group.

The intensity of functional connectivity was classified as state 0–4, which grows with increasing quantitative value (Fig. 3a). To examine the temporal trends of these FC states, we used the occurrence as a function of time, defined as the ratio of each state presented in the current time window. We found that the occurrence of state 1 in the non-relapse group tended to be higher than in the relapse group at each corresponding time, while the occurrences of state 3 and state 4 were lower (Fig. 3b). The proportion of state 1 in the relapse group was significantly decreased compared with the non-relapse group, while the proportion of state 3 was significantly increased ($p < 0.05$, Fig. 3c). There were significant correlations (corrected by Benjamini–Hochberg procedure) between BASED score and the proportion of functional connectivity (FC) states, particularly states 1 and 3 (Fig. 3d).

Table 3 Logistic regression analysis of relapse risk factors in children with infantile spasms who achieved short-term response

	OR	95% confidence interval		p
		Lower	Upper	
Model 1: univariate logistic regression analysis				
Gender (male/female)	0.6	0.21	1.67	0.33
Presence of hypsarrhythmia before ACTH treatment	0.39	0.079	1.47	0.19
Pathogenic structural abnormalities on MRI	0.97	0.29	3.33	0.95
Definitive etiology	2	0.73	5.65	0.18
Number of ASMs	1.5	0.73	3.26	0.28
VPA exposure history	2.79	1	8.3	0.055
TPM exposure history	1	0.19	5.1	0.97
VGB exposure history	0.35	0.016	3.8	0.4
Hormonal therapy history	1.25	0.28	6.58	0.77
Presence of hypsarrhythmia after ACTH treatment	5.03	0.79	98.3	0.146
Interval from onset to receive ACTH treatment	1.16	0.99	1.43	0.1
Age at spasm onset	1.09	0.91	1.35	0.4
Frequency of spasms	0.99	0.98	1	0.22
Dosage of ACTH	0.69	0.2	2.26	0.54
BASED score	2.26	1.54	3.62	**< 0.001**
Model 2: multivariate logistic regression analysis				
Presence of hypsarrhythmia after ACTH	1.37	0.1	37	0.8
Definitive or unknown etiology	1.26	0.31	4.87	0.7
VPA exposure history	3.41	0.93	14.4	0.074
Interval from onset to receive ACTH treatment	1.03	0.79	1.4	0.9
Presence of hypsarrhythmia before ACTH treatment	0.49	0.07	3.29	0.5
BASED score	2.23	1.43	3.83	**0.001**

ACTH adrenocorticotropic hormone, *ASM* antiseizure medication, *BASED* Burden of Amplitudes and Epileptiform Discharges, *TPM* topiramate, *VGB* vigabatrin, *VPA* valproate

Bold *p*-value is statistically significant; data are expressed as number, mean standard deviation, or median (range)

DISCUSSION

Some previous studies suggested the EEG features could be associated with the relapse of IS [7–10, 20]. Hayashi et al. demonstrated that serial EEG findings after ACTH therapy were significantly related to relapse; the persistence or worsening of epileptic discharges on EEG, especially multifocal epileptic discharges, may indicate a relapse [20]. Tanritanir et al. proposed that the reduction of delta power and delta coherence were greater in sustained responders

Table 4 Cox regression analysis of relapse risk factors in children with 64 infantile spasms who achieved a short-term response

	HR	95% confidence interval		p
		Lower	Upper	
Model 1: univariate cox regression analysis				
Gender (male/female)	0.73	0.37	1.46	0.4
Presence of hypsarrhythmia before ACTH treatment	0.58	0.27	1.23	0.2
Pathogenic structural abnormalities on MRI	0.93	0.42	2.03	0.9
Definitive etiology	1.57	0.82	3	0.2
Number of ASMs	1.44	0.91	2.28	0.12
VPA exposure history	1.97	1.03	3.77	**0.041**
TPM exposure history	0.89	0.31	2.51	0.8
VGB exposure history	0.5	0.07	3.68	0.5
Hormonal therapy history	1.03	0.4	2.64	0.91
Presence of hypsarrhythmia after ACTH treatment	3.18	1.31	7.71	**0.011**
Interval from onset to receive ACTH treatment	1.09	1	1.19	0.45
Age at spasm onset	1.04	0.94	1.15	0.5
Frequency of spasms	1	0.99	1	0.3
Dosage of ACTH (IU/kg)	0.87	0.39	1.95	0.7
BASED score	1.56	1.28	1.89	**< 0.001**
Model 2: multivariate COX regression analysis				
Definitive etiology	1.24	0.59	2.63	0.6
Presence of hypsarrhythmia after ACTH treatment	2.31	0.8	6.7	0.12
VPA exposure history	1.65	0.77	3.62	0.2
Interval from onset to receive ACTH treatment	0.96	0.86	1.08	0.5
Presence of hypsarrhythmia before ACTH treatment	0.67	0.26	1.69	0.4
Number of ASMs	1.45	0.84	2.51	0.2
BASED score	1.48	1.18	1.87	**< 0.001**

ACTH adrenocorticotropic hormone, *ASM* antiseizure medication, *BASED* burden of amplitudes and epileptiform discharges, *TPM* topiramate, *VGB* vigabatrin, *VPA* valproate

Bold *p*-value is statistically significant

than in relapsed patients or non-responders with IS treated by ACTH [8]. Wang et al. showed that, after ACTH treatment, the number and channels of high-frequency oscillations (HFOs) were significantly lower, whereas the percentage decrease in the number, spectral power, and channels of ripples was significantly higher in the seizure-free group than in the non-seizure-free group; meanwhile, the relapse subgroup showed a higher number, spectral
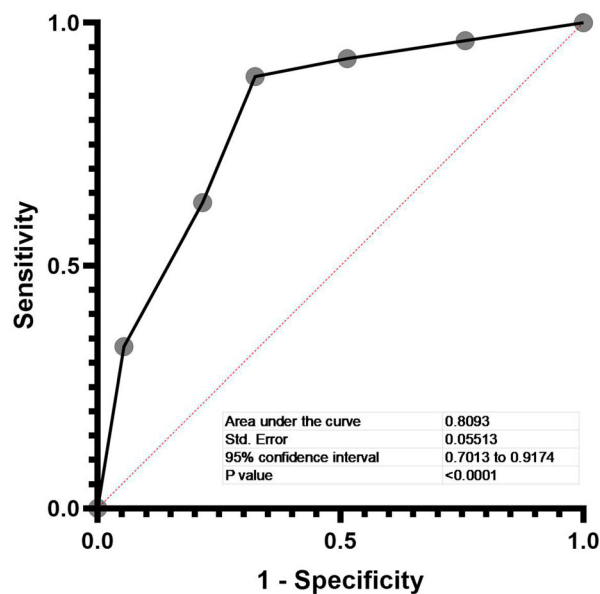
Fig. 1 Receiver operating characteristic (ROC) curves of the BASED score for relapse in the patient with a short-term response after ACTH treatment

power, and wider distribution of ripples than did the non-relapse subgroup [9]. The above studies suggest that EEG features are closely related to the relapse of IS.

In the presented study, the EEG results of children with short-term response after ACTH treatment were evaluated by the BASED scoring method, and we found the BASED score was higher in the relapse group than in the non-relapse group. This suggests that those who have a BASED score of 3 or higher have a high risk of relapse even they achieve a short-term response.

Although the disappearance of hypsarrhythmia is traditionally considered to be an important indicator of clinical efficacy and prognosis, its assessment exhibits poor inter-rater reliability [21]. Some children with IS did not present the typical EEG features [22, 23]. A recent study showed that, among 30 children with IS who experienced relapse, 26 children did not have the typical or modified hypsarrhythmia after ACTH treatment, which suggests that the relapse was not correlated with the presence or absence of hypsarrhythmia [8]. The

presence or absence of hypsarrhythmia after ACTH treatment was also investigated in our study; like in the previous study [8], there were no significant differences between the relapse group and non-relapse group. For this reason, hypsarrhythmia after ACTH treatment was not included in the final regression analysis.

Previous studies of IS have suggested it to be an age-related epileptic syndrome with transient age-specific neuronal hyperexcitability [24]. This nature of the disease is one of the hypothesized reasons for the permanent effect of short-course hormonal therapy, even after withdrawal of ACTH treatment [25, 26]. Experience over the past decades has indicated that, if the etiology remains unknown and there is normal psychomotor development before spasm onset, the patient will become seizure free and have normal or nearly normal development in about 80% cases [27–30], showing that epileptiform activity had been well controlled and the emergence of epileptic encephalopathy was prevented. In our study, the BASED score in the relapse group was higher than in the non-relapse group. As is the nature of the BASED scoring method, the higher the score, the more likely that spasms occur [12]. For this reason, a functional connectivity measure alongside BASED scoring, which showed that the relapse group had stronger, more stable functional networks than the non-relapse group; meanwhile, there were strong associations between the proportions of different functional connectivity intensity and BASED score. Shrey et al. [31] showed that all responders with epileptic spasms exhibited decreases in functional connectivity strength after treatment initiation, while an increase in connectivity strength occurred only in the non-responders. Therefore, we speculate that the significantly higher BASED score observed in the relapse group indicates that the epileptiform activity in those children was not sufficiently and effectively controlled, which led to relapse after short-term response.

The combination of personal history, physical examination, and early imaging yields an identifiable etiology in about 40–55% of cases of IS [1, 32, 33]. There were 46.9% patients with a definitive etiology and 53.1% patients with an
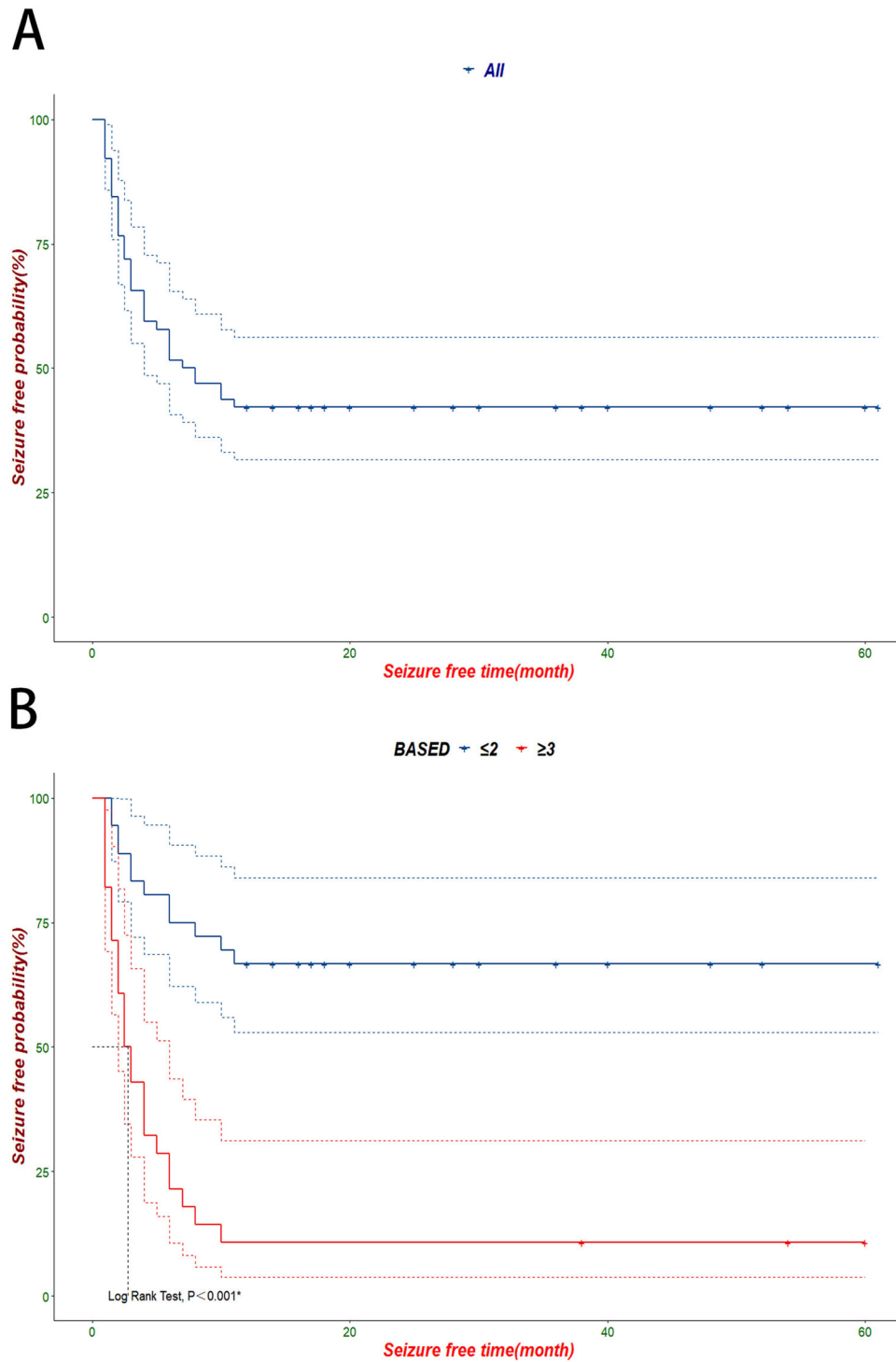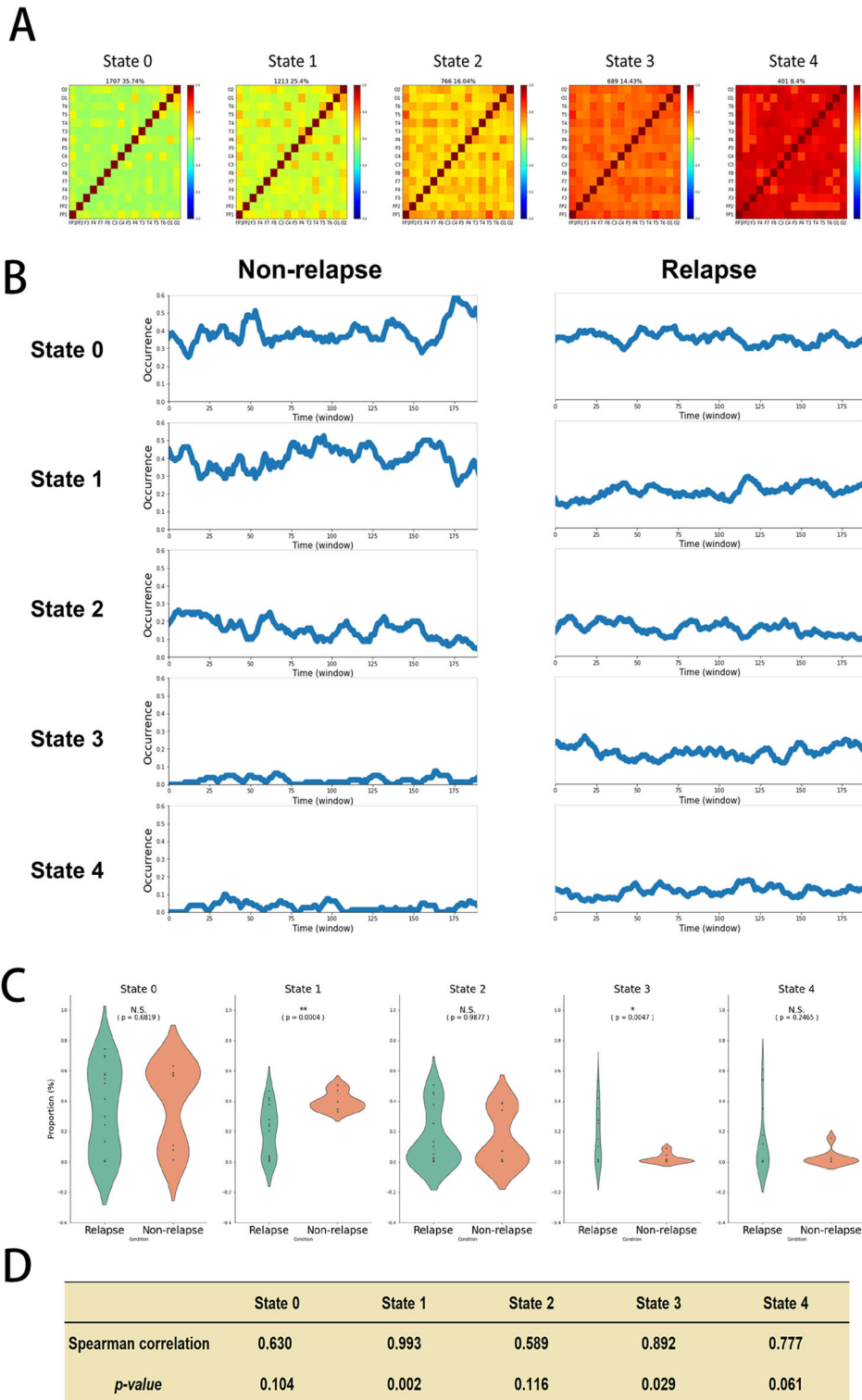
Fig. 2 Kaplan–Meier (KM) survival curves for the patients with a short-term response after ACTH treatment. **A** Survival curves for the patients with a short-term response after ACTH treatment. **B** Survival curves with a cutoff value of BASED score (≥ 3 or ≤ 2) for the patients with a short-term response after ACTH treatment

◄**Fig. 3** Functional connectivity measure of 24 patients. **A** Functional connectivity states: red, stronger; green, weaker. **B** Occurrences of each state during the BASED scoring duration in the non-relapse and relapse group separately. **C** State 0–4 comparisons between non-relapse and relapse group. **D** Correlations between states and BASED score

unknown etiology in our cohort, which was consistent with previous studies. The etiology (definitive versus unknown) did not differ significantly between the relapse group and the non-relapse group, and it did not have a significant effect on relapse or non-relapse in Cox proportional hazards regression models, which was in line with a recent study by Hayashi et al. [20]. In addition, etiology (definitive versus unknown) is not associated with the BASED score after ACTH treatment. However, it needs to be noted that there was a relatively long time (about 10 years) to accrue patients included in our cohort; thus, owing to the low prevalence of molecular diagnostic techniques in the past, some patients with definitive etiology could have been mistakenly assigned as unknown cases.

Several studies have shown that patients with structural anomalies on MRI have a poor prognosis, such as a lower incidence of short-term response and long-term seizure freedom [6, 33]. In our cohort, all children underwent brain MRI examination. The presence or absence of pathogenic structural abnormalities on MRI did not differ significantly between the relapse group and non-relapse group, and it also did not have a significant effect in Cox proportional hazards regression models.

In line with the previous study [6], the interval from ACTH treatment to relapse was 3 (1.5, 6) months in our study. The rate of relapse in our cohort was 57.8%, which is higher than in previous studies [6, 20, 34–36]. This may have been caused by the strict inclusion criteria, which were implemented to avoid missing subtle spasms that are difficult to identify (such as episodes of yawning, gasping, facial grimacing, isolated eye movements, and transient focal motor activity). Only the patients with non-relapse who were readmitted to our

hospital could be included, which also may have led to some patients with non-relapse being excluded .

Our study also has some limitations. The strength of the conclusions of this study was limited by its sample size. In addition, there was also potential bias generated during patient selection owing to the strict inclusion and exclusion criteria. Finally, we did not perform a more detailed classification of etiology. Future studies are needed to overcome these limitations, and we hope our study will motivate other investigators to replicate and extend these findings.

CONCLUSION

In conclusion, our study suggests that the BASED score after ACTH treatment may be predictive of relapse after short-term response. Patients with IS who have a BASED score greater than or equal to 3 seem to have a higher risk of relapse, and they may exhibit EEG abnormal functional connections.

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Compliance with Ethics Guidelines. This study was approved by the Ethics Committee of First Medical Center of PLA General Hospital (S2021-569-01). This study was a retrospective cohort study, patient identity remained nnonymous, and the requirement for informed consent was waived by the Ethics Committee of First Medical Center of PLA General Hospital due to the observational nature of the study (S2021-569-01).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Lux AL, Osborne JP. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. Epilepsia. 2004;45: 1416–28.

2. Callaghan FJ, Edwards SW, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. Lancet Neurol. 2017;16:33–42.

3. Callaghan F, Edwards SW, et al. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. Lancet Child Adolesc Health. 2018;2:715–25.

4. Riikonen RS. Favourable prognostic factors with infantile spasms. Eur J Paediatr Neurol. 2010;14: 13–8.

5. Shields WD. Infantile spasms: little seizures, BIG consequences Epilepsy Curr. 2006;6:63–9.

6. Riikonen R. Infantile spasms: outcome in clinical studies. Pediatr Neurol. 2020;108:54–64.

7. Dressler A, Benninger F, Trimmel-Schwahofer P, et al. Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: a single-center parallel-cohort randomized controlled trial. Epilepsia. 2019;60: 441–51.

8. Tanritanir A, Vieluf S, Jafarpour S, et al. EEG biomarkers of repository corticotropin injection treatment. J Clin Neurophysiol. 2021.

9. Wang W, Li H, Yan J, et al. Automatic detection of interictal ripples on scalp EEG to evaluate the effect and prognosis of ACTH therapy in patients with infantile spasms. Epilepsia. 2021;62:2240–51.

10. Yan L, Li L, Chen J, et al. Application of high-frequency oscillations on scalp EEG in infant spasm: a prospective controlled study. Front Hum Neurosci. 2021;15:682011.

11. Yuskaitis CJ, Mysak K, Godlewski B, et al. Confirmation of infantile spasms resolution by prolonged outpatient EEGs. Epilepsia Open. 2021.

12. Mytinger JR, Vidaurre J, Moore-Clingenpeel M, et al. A reliable interictal EEG grading scale for children with infantile spasms—the 2021 BASED score. Epilepsy Res. 2021;173:106631.

13. Yin J, Lu Q, Yin F, et al. Effectiveness and safety of different once-daily doses of adrenocorticotropic hormone for infantile spasms. Paediatr Drugs. 2017;19:357–65.

14. Wan L, Li Z, Sun Y, et al. Clinical characteristics and treatment outcomes of pediatric patients with postencephalitic epilepsy characterized by epileptic spasms. Seizure. 2021;84:116–21.

15. Bowen M, Peragallo JH, Kralik SF, et al. Magnetic resonance imaging findings in children with spasmus nutans. J AAPOS. 2017;21:127–30.

16. Trowbridge SK, Yuskaitis CJ, Baumer N, et al. Brain MRI abnormalities in patients with infantile spasms and Down syndrome. Epilepsy Behav. 2019;92: 57–60.

17. Harini C, Sharda S, Bergin AM, et al. Detailed magnetic resonance imaging (MRI) analysis in infantile spasms. J Child Neurol. 2018;33:405–12.

18. Hrachovy RA, Frost JD Jr, Kellaway P. Hypsarrhythmia: variations on the theme. Epilepsia. 1984;25:317–25.

19. Asadi-Pooya AA, Dlugos D, Skidmore C, et al. Atlas of electroencephalography, 3rd edition. Epileptic Disord. 2017;19:384.

20. Hayashi Y, Yoshinaga H, Akiyama T, et al. Predictive factors for relapse of epileptic spasms after adrenocorticotropic hormone therapy in West syndrome. Brain Dev. 2016;38:32–9.

21. Hussain SA, Kwong G, Millichap JJ, et al. Hypsarrhythmia assessment exhibits poor interrater reliability: a threat to clinical trial validity. Epilepsia. 2015;56:77–81.

22. Lee YJ, Berg AT, Nordli DR Jr. Clinical spectrum of epileptic spasms in children. Brain Dev. 2015;37: 37–48.

23. Vendrame M, Guilhoto LM, Loddenkemper T, et al. Outcomes of epileptic spasms in patients aged less than 3 years: single-center United States experience. Pediatr Neurol. 2012;46:276–80.

24. Choi HS, Ko A, Kim SH, et al. Disparate treatment outcomes according to presence of pathogenic mutations in West syndrome. Epilepsia. 2021;62: 1656–64.

25. Dulac O. What is West syndrome. Brain Dev. 2001;23:447–52.

26. Brunson KL, Eghbal-Ahmadi M, Baram TZ. How do the many etiologies of West syndrome lead to excitability and seizures? The corticotropin releasing hormone excess hypothesis. Brain Dev. 2001;23:533–8.

27. Cohen-Sadan S, Kramer U, Ben-Zeev B, et al. Multicenter long-term follow-up of children with idiopathic West syndrome: ACTH versus vigabatrin. Eur J Neurol. 2009;16:482–7.

28. Kivity S, Lerman P, Ariel R, et al. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Epilepsia. 2004;45: 255–62.

29. Granström ML, Gaily E, Liukkonen E. Treatment of infantile spasms: results of a population-based study with vigabatrin as the first drug for spasms. Epilepsia. 1999;40:950–7.

30. Gaily E, Lommi M, Lapatto R, et al. Incidence and outcome of epilepsy syndromes with onset in the first year of life: a retrospective population-based study. Epilepsia. 2016;57:1594–601.

31. Shrey DW, Kim McManus O, Rajaraman R, et al. Strength and stability of EEG functional connectivity predict treatment response in infants with epileptic spasms. Clin Neurophysiol. 2018;129: 2137–48.

32. Wirrell EC, Shellhaas RA, Joshi C, et al. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia. 2015;56: 617–25.

33. Messer R, Knupp KG. Infantile spasms: opportunities to improve care. Semin Neurol. 2020;40: 236–45.

34. Hrachovy RA, Frost JD Jr, Kellaway P, et al. Double-blind study of ACTH vs prednisone therapy in infantile spasms. J Pediatr. 1983;103:641–5.

35. Rajaraman RR, Lay J, Alayari A, et al. Prevention of infantile spasms relapse: zonisamide and topiramate provide no benefit. Epilepsia. 2016;57:1280–7.

36. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2012;78:1974–80.