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Long-term seizure outcome in patients with status epilepticus due to acute encephalitis

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ABSTRACT

Purpose: To investigate the long-term seizure outcome in patients with convulsive status epilepticus (CSE) due to acute encephalitis and identify early predictors for terminal seizure remission.

Methods: Based on a prospective registry of CSE, consecutive patients with CSE due to acute encephalitis were enrolled from July 2009 to November 2017, with follow-up ending in November 2018. Variables during hospital stay, seizure outcomes within 1 month after status epilepticus (SE), and seizure outcomes within 3 months after acute phase of encephalitis were assessed for predicting terminal seizure freedom.

Results: After a median 58-month observation period, 77 patients were included in this study. Twenty-eight (36%) patients died within 3 months, 22 (29%) patients had recurrent seizures after acute phase of encephalitis, and 27 (35%) patients attained terminal seizure freedom after acute phase of encephalitis. Patients with CSE due to autoimmune encephalitis had a higher rate of terminal seizure freedom than those with viral and other encephalitis. Among all living patients (n = 49), 26 (53%) patients were on anti-epileptic medication at the end of follow-up. STESS score on admission, seizure freedom throughout 1 month after SE, and seizure freedom throughout 3 months after acute phase were found to be independently associated with terminal seizure freedom.

Conclusions: Our study proposed a dynamic assessment system to identify patients for whom long-term use of anti-epileptic drugs (AEDs) might not be necessary. Our findings filled a gap in treatment decision on how long AEDs should be continued for patients with CSE due to acute encephalitis.

1. Introduction

Encephalitis is swelling and inflammation of the brain, which can be caused by infectious or autoimmune aetiologies. Up to 18.5%–40.4% of patients were reported to develop status epilepticus (SE) during the acute stage of encephalitis and received anti-epileptic treatments [1–3]. To prevent recurrent seizures, anti-epileptic drugs (AEDs) are usually continued for a long time after the remission of acute SE. However, some patients will never have unprovoked seizures after the acute phase of encephalitis [3–5], and long-term anti-epileptic treatment may not be necessary for them.

To date, few studies have evaluated long-term seizure outcomes in patients with SE due to acute encephalitis. Clinicians are often faced with a decision-making dilemma when they attempt to continue or discontinue the use of AEDs after the acute phase. The long-term use of AEDs can prevent possible unprovoked seizures in the future, but it may also reduce the quality of life in seizure-free patients [6]. In this study, we evaluated long-term seizure outcome in patients with SE due to

Abbreviations: SE, status epilepticus; AEDs, anti-epileptic drugs; CSE, convulsive status epilepticus; N-ICU, neurological intensive care unit; EEG, electro-encephalogram; IV, intravenous; GCS, Glasgow Coma Scale; APACHEII, Acute Physiology and Chronic Health Evaluation; STESS, Status Epilepticus Severity Score; NCSE, non-convulsive status epilepticus; END-IT, encephalitis-NCSE-diazepam resistance-image abnormalities-tracheal intubation; PPV, positive predictive value; NPV, negative predictive value; HSE, herpes simplex virus encephalitis; anti-NMDAR, anti-N-methyl-D-aspartate receptor; RSE, refractory status epilepticus; SRSE, super-refractory status epilepticus; IV AEDs, intravenous anti-epileptic drugs

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acute encephalitis and investigated the early predictors for terminal seizure remission to identify the patients who may not require long-term use of AEDs after the acute phase.

2. Methods

2.1. Study design

This is a retrospective study based on a prospective registry of patients with convulsive status epilepticus (CSE) who were admitted to the neurological intensive care unit (N-ICU) of Xijing Hospital, China, a tertiary academic medical centre. This study was fully approved by the ethics committee of Xijing Hospital (KY20182024-F-1) and was in compliance with Chinese laws and the Helsinki Declaration. All patients or their surrogate care providers provided informed consent before they were included in this study.

2.2. Patients

From July 2009 to November 2017, consecutive patients diagnosed with CSE due to acute encephalitis (≥ 12 years of age) were included in this study. CSE was defined as 5 min or more of continuous motor seizure activity or recurrent seizure activity without regaining full consciousness between episodes [7]. CSE included both focal convulsive SE and generalised tonic-clonic SE. Acute encephalitis was defined as altered mental status (decreased or altered level of consciousness, lethargy, or personality change) lasting more than 24 h, with at least three of the following associated manifestations: (1) fever of 38 °C or higher within 72 h before or after presentation, (2) generalised or partial seizures, (3) new onset of focal neurologic findings, (4) cerebrospinal fluid (CSF) white blood cell count 5/mm^3 or higher, (5) abnormality of brain parenchyma on neuroimaging, and (6) electroencephalogram (EEG) abnormality [8]. Patients with a history of epilepsy were excluded. Case eligibility was determined by a study neurologist based on the clinical records, neuroimaging and EEG findings.

2.3. Management

All participants received anti-SE treatments from the same group of neurologists according to the clinical guidelines [9–12]: the first-line agents were benzodiazepines; the second-line treatment was intravenous (IV) sodium valproate or phenobarbital sodium; and the third-line treatment was continuous infusion of anaesthetics (midazolam or/and propofol). All the patients were monitored continuously using a bedside video-EEG with an array of 20 scalp electrodes (Solar 2000 N, Solar Electronic Technologies Co., Ltd., Beijing, China) for at least 24 h to guide anti-epileptic treatments and detect the presence of non-convulsive seizures. All patients were taking oral anti-epileptic drugs (AEDs) when they were discharged from the N-ICU.

2.4. Data collection

The following variables that may predict the long-term seizure outcomes of patients with SE due to encephalitis were collected for statistical analysis: (1) demographics; (2) time from onset of encephalitis to the diagnosis of SE and to N-ICU admission; (3) illness severity including Glasgow Coma Scale (GCS) and Acute Physiology and Chronic Health Evaluation (APACHEII) on admission; (4) SE severity including Status Epilepticus Severity Score (STESS), encephalitis-NCSE-diazepam resistance-image abnormalities-tracheal intubation (END-IT) score [13], serum albumin [14], refractory SE, super-refractory SE, and the complication of non-convulsive status epilepticus (NCSE); (5) aetiology of acute encephalitis; (6) treatments in N-ICU including intubation, number of IV AEDs, length of N-ICU stay, and number of oral AEDs at hospital discharge; and (7) neuroimaging and EEG findings. Abnormal brain magnetic resonance imaging (MRI) findings were defined as hypointensity on T1-weighted images (T1WI) and hyperintensity on T2-weighted images (T2 WI) and fluid-attenuated inversion recovery (FLAIR). The results of the last continuous EEG monitoring before N-ICU discharge were used for the analysis and were grouped into the following: (1) normal, (2) diffuse or focal slow waves, and (3) epileptiform activity. When both diffuse/focal slow waves and epileptiform activity were found in one patient, it was recorded as epileptiform activity. Seizure outcomes in the following two observation periods were also determined and analysed as potential predictors for terminal seizure freedom after each observation period: (1) within 1 month after SE and (2) within 3 months after the acute phase. Seizures occurring within 1 month after SE were likely to be provoked, whereas seizures occurring after the acute phase were usually unprovoked, and the predictive values of them might be different [15–18]. The acute phase of encephalitis was defined as the first 3 months after the disease onset based on the characteristics of autoimmune encephalitis, which usually has a longer acute phase than other encephalitis [3,19]. The exact diagnoses of encephalitis were made according to our previous published study based on related guidelines or consensuses [19–21].

2.5. Outcome assessment

Seizure outcomes were first assessed at 6 months after N-ICU discharge to determine whether there were seizures occurring during the two observation periods (within 1 month after SE and within 3 months after the acute phase) by a trained neurologist based on clinical data during the N-ICU stay, telephone interviews, and routine clinical follow-ups. Then long-term seizure outcome was assessed independently in November 2018, 12 months after the SE onset of the last enrolled patient, by another trained neurologist based on telephone interviews and routine clinical follow-ups. Terminal seizure freedom was defined as sustained freedom from all seizures, including auras, until the last follow-up.

2.6. Statistical analysis

Univariate logistic regression models were used to search for early in-hospital predictors of terminal seizure freedom after the acute phase of encephalitis. Multivariate logistic regression models were used to examine the relationships between seizure outcomes during two observation periods and terminal seizure freedom after them, adjusted for demographics (age, sex) and SE severity (STESS score). Seizure outcome in each observation period was summarised into two indicators. For the first observation period (within 1 month after SE), seizure frequencies within the first 2 weeks after SE and throughout 1 month after SE were analysed; for the second observation period (within 3 months after acute phase), seizure frequencies within the first month after acute phase and throughout 3 months after the acute phase were analysed. The specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the in-hospital predictor (STESS score) and indicators in two observation periods were calculated. Two-sided p values < 0.05 were considered significant. Statistical analyses were conducted with SPSS version 22 software (SPSS Inc., Chicago, IL, United States).

3. Results

3.1. Demographic and clinical characteristics

From July 2009 to November 2017, a total of 88 patients with SE due to acute encephalitis were identified. Ten patients who were lost to follow-up were excluded, and one patient with a history of epilepsy was excluded. Eventually, a total of 77 patients were included in this study (Supplementary figure S1). The median patient age was 31 years

Table 1
Demographic and Clinical Characteristics.

Variables	Total (n = 77)
Age (years)	31 (19–45)
Sex (male)	44 (57.1%)
Time from encephalitis onset to SE (days)	6 (3–13)
Time from encephalitis onset to admission (days)	10 (7–20)
GCS on admission	9 (6–12)
APACHEII on admission	9 (5–13)
STESS	3 (3–4)
END-IT score	4 (3–5)
Serum albumin on admission	39.4 (36.0–42.4)
RSE	35 (45.5%)
SRSE	19 (24.7%)
Complicated with NCSE	44 (57.1%)
Aetiology of encephalitis	
Autoimmune	16 (20.8%)
Viral	31 (40.3%)
Unknown	26 (33.8%)
Other[a]	4 (5.2%)
Intubation	42 (54.5%)
Number of IV AEDs	2 (1–3)
N-ICU length of stay (days)	19 (10–32)
Number of oral AEDs at hospital discharge	2 (1–3)
Brain image	
Normal	27 (35.1%)
Cortical or hippocampal involvement	16 (20.8%)
Exclusively abnormalities in other areas[b]	34 (44.1%)
EEG[c]	
Normal	8 (10.4%)
Diffuse or focal slow waves	33 (42.9%)
Epileptiform activity	36 (46.8%)

SE, status epilepticus; GCS, Glasgow Coma Scale; APACHEII, Acute Physiology and Chronic Health Evaluation; STESS, Status Epilepticus Severity Score; END-IT: encephalitis-NCSE-diazepam resistance-image abnormalities-tracheal intubation; RSE, refractory status epilepticus; SRSE, super-refractory status epilepticus; NCSE, nonconvulsive status epilepticus; IV AEDs, intravenous antiepileptic drugs.
Data were presented as n (%) or median (interquartile range).
[a] Includes bacterial (n = 2), cryptococcosis (n = 1), and neurosyphilis (n = 1).
[b] Brain parenchyma abnormalities except cortex and hippocampus. [c]The last continuous EEG monitoring before N-ICU discharge.

[interquartile range (IQR) :19-45 y], and 57.1% were male (Table 1). The median time from onset of encephalitis to SE and to N-ICU admission were 6 (IQR: 3-13) days and 10 (IQR: 7–20) days, respectively. The conditions of included patients were quite severe at N-ICU admission, reflected by a median GCS score of 9 and a median STESS score of 3. The aetiologies of encephalitis were autoimmune in 16 patients (20.8%), viral in 31 patients (40.3%), bacterial in 2 patients (2.6%), cryptococcosis in 1 patient (1.3%), neurosyphilis in 1 patient (1.3%), and unknown in 26 patients (33.8%). Twenty-seven (35.1%) patients had normal brain images, 16 (20.8%) patients had cortical or hippocampal abnormalities, and 34 (44.1%) patients had abnormalities exclusively in other areas that contain brain parenchyma, except the cortex and hippocampus.

3.2. Seizure outcomes

The median follow-up period was 58 months, ranging from 12 to 111 months. Twenty-eight (36%) patients died within 3 months; 22 (29%) patients had recurrent seizures after the acute phase of encephalitis; and 27 (35%) patients attained terminal seizure freedom after the acute phase of encephalitis (Fig. 1A). Patients with SE due to autoimmune encephalitis had a higher rate of terminal seizure freedom than patients with viral encephalitis and patients with other encephalitis (Fig. 1B). Among all the surviving patients (n = 49), 26 (53%) patients had one or more oral AEDs at the end of follow-up (Fig. 2A), and Levetiracetam had the highest terminal retention rate

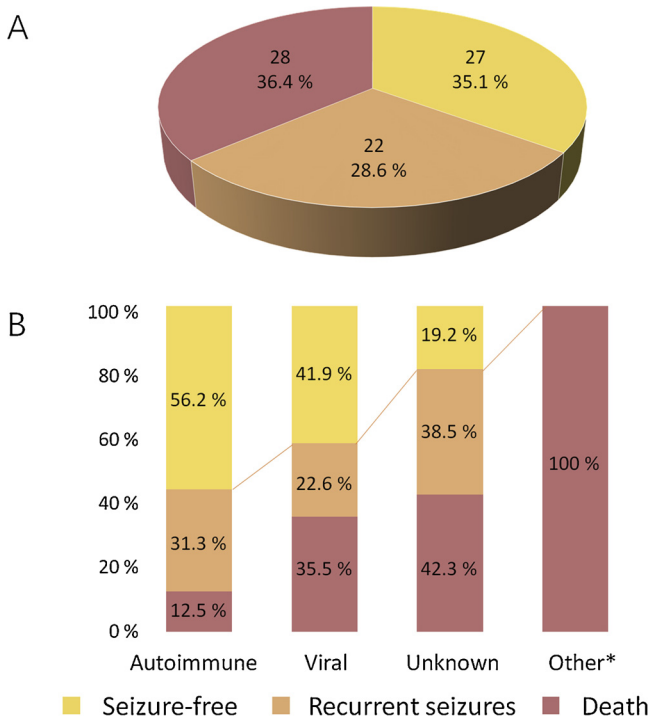

Fig. 1. Seizure outcome after the acute phase of encephalitis. (A) Total (n = 77); (B) According to aetiology, including autoimmune (n = 16), viral (n = 31), unknown (n = 26), and other (n = 4) causes. *Includes bacterial (n = 2), cryptococcosis (n = 1), and neurosyphilis (n = 1).

(Fig. 2B).

3.3. Indicators for seizure freedom

Table 2 showed that STESS score on N-ICU admission was the only in-hospital indicator that was significantly associated with terminal seizure freedom after the acute phase of encephalitis [odds ratio (OR) 5.88, 95% confidence interval (CI): 1.13–30.63, p = 0.04]. In the first observation period (within 1 month after SE), both seizure freedom within the first 2 weeks after SE (OR 17.98, 95%CI: 2.54–127.21, p = 0.004) and throughout 1 month after SE (OR 12.68, 95%CI 1.17–137.83, p = 0.04) were independently associated with terminal seizure freedom after them. In the second observation period (within 3 months after the acute phase), both seizure freedom within the first month after the acute phase (OR 72.73, 95%CI 6.56–806.74, p < 0.001) and throughout 3 months after the acute phase (OR 654.14, 95%CI 12.00–35665.22, p = 0.001) were independently associated with terminal seizure freedom after them as well.

The specificity, sensitivity, PPV, NPV, and accuracy of all five of the predictors are presented in Supplementary figure S2. Specificity was used as the key parameter to choose the better predictor during each observation period. A higher specificity means the better capacity to identify those patients who would have recurrent seizures; therefore, the discontinuation of AEDs in patients who really need long-term AEDs can be maximally avoided. In the end, three predictors for terminal seizure freedom in three phases were determined: STESS score on admission, seizure freedom throughout 1 month after SE, and seizure freedom throughout 3 months after the acute phase. These three predictors in three phases constituted a dynamic assessment system for identifying those patients who might not need long-term AEDs. As the earliest indicator, STESS score on admission identified 37% of patients who would stay seizure-free after the acute phase of encephalitis (sensitivity, Fig. 3). As time went on, the second predictor (seizure freedom throughout 1 month after SE) identified 44% of patients who would stay seizure-free after it; and the third predictor (seizure freedom

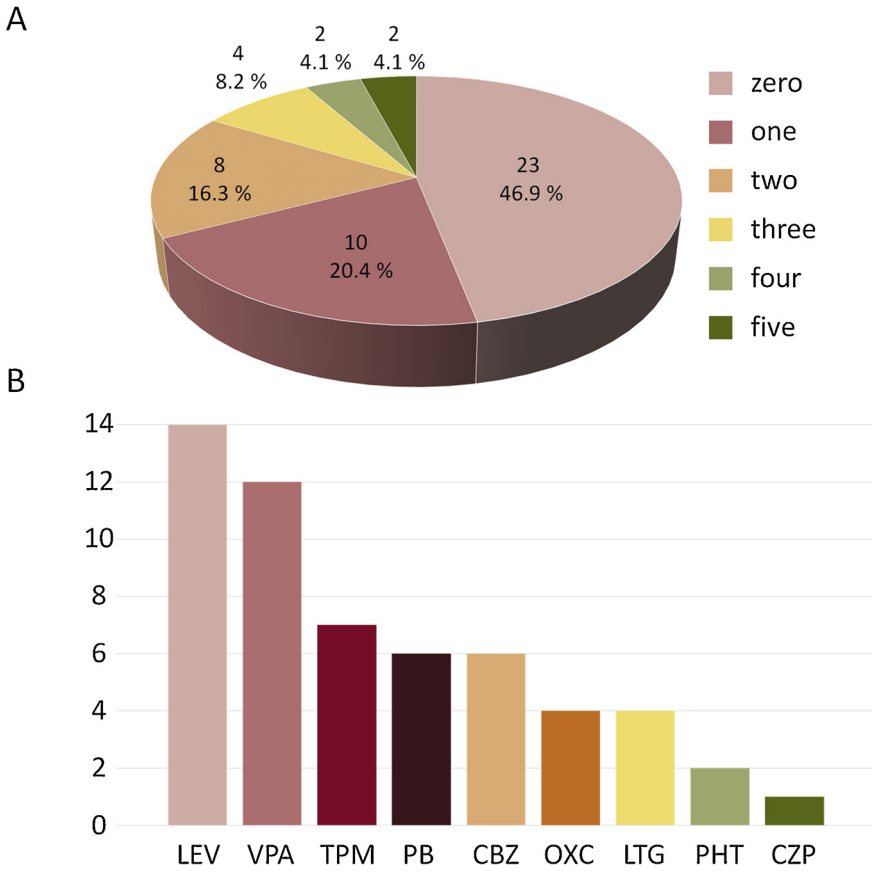

Fig. 2. Administration of AEDs in survivors at the end of follow-up (n = 49). (A) According to numbers of AEDs; (B) According to types of AEDs. LEV, levetiracetam; VPA, sodium valproate; TPM, topiramate; PB, phenobarbital; CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine; PHT, phenytoin; CZP, clonazepam.

throughout 3 months after acute phase) identified 87% (Table 3).

4. Discussion

Patients with symptomatic SE due to acute encephalitis have a high risk of developing postencephalitic epilepsy, but they may also never have recurrent seizures after the acute phase [3,4]. Identification of patients who will not develop postencephalitic epilepsy may avoid unnecessary long-term use of AEDs. After a median follow-up period of 58 months, we found that 35% of patients with SE due to acute encephalitis stayed seizure-free after the acute phase. A dynamic assessment to identify patients who may not need long-term anti-epileptic therapy was proposed with high specificity and PPV.

Previous studies have shown that in herpes simplex virus encephalitis (HSE), 55.5% to 70% of patients did not have recurrent seizures after recovery from the acute phase [22,23]. In anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, 81% of patients developed seizures at the acute phase, but more than 80% of patients with acute seizures had no seizures after 6 months from disease onset [3]. Our study included patients with CSE due to acute encephalitis, a cohort considered to have a higher potential risk of developing post-encephalitis, and found that there were still 35% of patients without any seizure after the acute phase of encephalitis. In our study, the risk of attaining seizure freedom after acute encephalitis varies partially depending on the aetiology: more patients with autoimmune encephalitis stayed seizure-free after the acute phase than patients with infectious encephalitis. This finding was consistent with a Chinese study on anti-NMDAR encephalitis [3] and needed to be proven in patients from other areas of the world.

Encephalitis caused by different aetiologies has different disease courses; therefore, the length of the acute phase of different encephalitis is also not the same. Infectious encephalitis generally has a more rapid onset and shorter hospital stay than autoimmune encephalitis [19,24–26]. Patients with viral encephalitis were usually admitted to hospital after 4 days from the disease onset and had a hospital stay of 14 to 22 days [23,27]; and, patients with anti-NMDAR encephalitis were admitted to hospital after 10 to 14 days from the onset and stayed in the hospital for approximately 3 months [28,29]. For the ease of analysis and to reduce a misdiagnosis rate of unprovoked seizures, which are an important index for the diagnosis of post-encephalitic epilepsy, in this study we defined the acute phase of all types of encephalitis as the first 3 months from the disease onset based on the characteristics of autoimmune encephalitis [3,19].

The occurrence of SE in acute encephalitis was reported to be a predictor of remote recurrent seizures [3,4]. However, in encephalitis patients with SE, our study showed that the refractoriness of SE (RSE or SRSE) was not closely related to recurrent seizures after the acute phase of encephalitis. In this study, many patients with non-refractory SE also developed subsequent unprovoked seizures; therefore, the refractoriness of SE cannot be used as a reliable predictor for the recurrence of seizures after the acute phase of encephalitis.

To prevent recurrent seizures, AEDs were usually used for a long time in patients with acute symptomatic SE. However, the timing for withdrawing AEDs after the acute phase was unclear due to lack of clinical evidence. One reason for the difficulty in determining the perfect withdrawal timing is that it is impossible to find out when exactly the reversible or temporary factors lowering the threshold and generating seizures were eliminated [30]. Another reason is that it is difficult to identify those encephalitis patients without long-lasting brain lesions that may trigger seizures in the future. Some types of encephalitis, such as anti-NMDAR encephalitis and HSE, may have relapses and cause symptomatic seizures again [31–37].

Table 2
Univariate analysis of in-hospital predictors for terminal seizure freedom after the acute phase of encephalitis.

Variables	OR	95%CI	*p*-value
Age (years)	1.00	0.96–1.03	0.86
Sex (male)	0.64	0.21–2.00	0.45
Time from encephalitis onset to admission (days)	0.97	0.93–1.11	0.23
Time from encephalitis onset to SE (days)	0.98	0.95–1.02	0.33
GCS on admission	1.14	0.96–1.35	0.13
APACHEII on admission	0.89	0.78–1.01	0.07
STESS < 3	5.88	1.13–30.63	0.04
END-IT score < 3	5.00	0.95–26.28	0.06
Serum albumin on admission	1.10	0.98–1.23	0.11
RSE	0.57	0.18–1.79	0.34
SRSE	0.33	0.07–1.53	0.16
Complicated with NCSE	0.39	0.12–1.25	0.11
Aetiology of encephalitis			
Autoimmune	1		
Viral	1.03	0.25–4.30	0.97
Unknown	0.28	0.06–1.29	0.10
Other[a]	–	–	–
Intubation	0.61	0.19–2.00	0.41
Number of IV AEDs	0.73	0.41–1.29	0.28
N-ICU length of stay (days)	0.98	0.95–1.01	0.11
Number of oral AEDs at hospital discharge	0.60	0.33–1.08	0.09
Brain image			
Normal	1		
Cortical or hippocampal involvement	0.49	0.11–2.20	0.49
Exclusively abnormalities in other areas[b]	0.65	0.18–2.37	0.65
EEG[c]			
Normal	1		
Diffuse or focal slow waves	0.15	0.01–1.50	0.11
Epileptiform activity	0.28	0.03–2.78	0.28

SE, status epilepticus; GCS, Glasgow Coma Scale; APACHEII, Acute Physiology and Chronic Health Evaluation; STESS, Status Epilepticus Severity Score; END-IT: encephalitis-NCSE-diazepam resistance-image abnormalities-tracheal intubation; RSE, refractory status epilepticus; SRSE, super-refractory status epilepticus; NCSE, nonconvulsive status epilepticus; IV AEDs, intravenous anti-epileptic drugs.

[a] Includes bacterial (n = 2), cryptococcosis (n = 1), and neurosyphilis (n = 1).

[b] Brain parenchyma abnormalities except cortex and hippocampus. [c]The last continuous EEG monitoring before N-ICU discharge.

In this study, STESS score on admission and seizure outcomes in two observation periods were proposed for the prediction of terminal seizure freedom. The STESS score was originally designed for predicting mortality in SE [38], and our study showed that it also had very good specificity for identifying patients who would have terminal seizure freedom after the acute phase of encephalitis. Staying seizure-free within the first month after the first episode of SE produced the highest specificity, meaning it had the fewest patients who had been considered terminally seizure-free by mistake. Staying seizure-free within the first 3 months after the acute phase of encephalitis produced the highest PPV, which means the highest accuracy of identifying those patients who would not have seizures later. Since STESS score and seizure outcomes of two observation periods were not evaluated at the same time, clinicians can assess patients dynamically to identify as early as possible patients who may not need long-term use of AEDs: STESS score < 3 (on admission) identified only 37.0% of patients who stayed seizure-free after the acute phase; seizure freedom within the first month after SE identified 44.4% of patients who had no recurrent seizures later; and seizure freedom within the first 3 months after the acute phase identified 87.1% of patients who had terminal seizure freedom after it.

There are some limitations in this study. First, this is a single-centre research with a limited sample size. However, even with such a small sample that is unable to detect small difference, we managed to identify several predictors that were significantly associated with terminal seizure freedom. Second, for those patients who had no remote recurrent seizures in this study, it is very difficult for us to tell whether it was because of the efficacy of AEDs or the elimination of epileptogenic factors. Future studies with a randomised and controlled setting may provide more solid evidence. Third, this study included very few patients with bacterial encephalitis; therefore, the applicability of conclusions we proposed needs to be further confirmed in bacterial encephalitis. Moreover, this is a study of adult patients, and long-term seizure outcomes in children with acute encephalitis may be different due to their immature brains.

5. Conclusion

Patients with SE due to autoimmune encephalitis had a higher rate of terminal seizure freedom than those with viral encephalitis and other encephalitis. A dynamic assessment for patients with SE due to acute encephalitis was proposed to identify those patients who may not need long-term use of AEDs: STESS score on admission, seizure outcome within the first month after SE, and seizure outcome within the first 3 months after the acute phase. Our findings filled a gap in treatment decision making and patient counselling on how long anti-epileptic therapy should be used in patients with SE due to acute encephalitis.

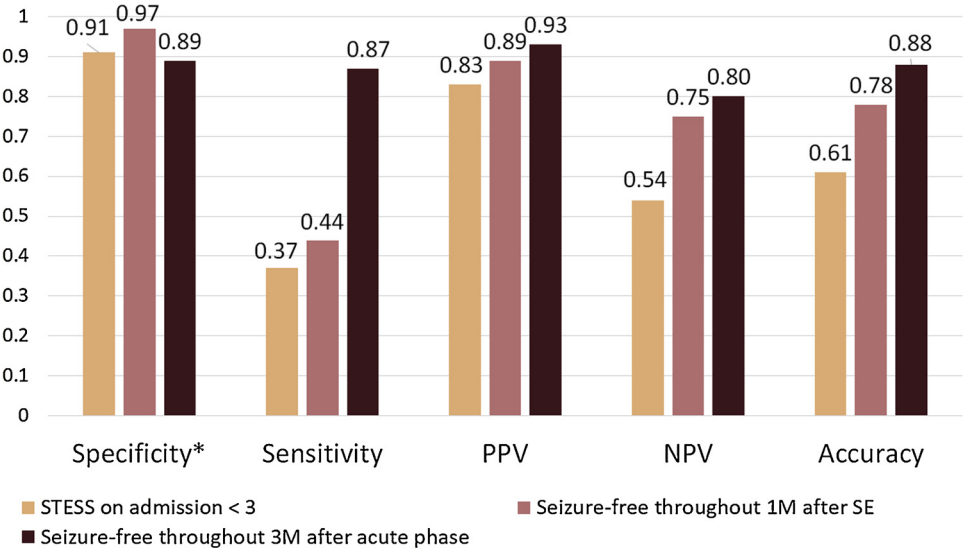

Fig. 3. Specificity, sensitivity, PPV, NPV, and accuracy of the three indicators for predicting terminal seizure freedom. PPV, positive predictive value; NPV, negative predictive value; M, month. *The higher value means the better capacity to identify those patients who would have recurrent seizures and avoid unnecessary discontinuation of anti-epileptic treatment.

Table 3
Multivariate analysis of seizure outcomes in different observation periods for predicting terminal seizure freedom.

Observation periods*	OR	95%CI	*p*-value
Seizure free within 1 M after SE			
within the first 2 W after SE	17.98	2.54–127.21	0.004
throughout 1 M after SE	12.68	1.17–137.83	0.04
Seizure free within 3 M after acute phase			
Within the first month after acute phase	72.73	6.56–806.74	< 0.001
throughout 3 M after acute phase	654.14	12.00–35,665.22	0.001

SE, status epilepticus; M, month; W, week.
* Adjusted with age, sex, and STESS.

Declarations of interest

None of the authors has any conflict of interest to disclose.

Author contributions

XXL: Study design, data acquisition, analysis of data, drafting of the manuscript. FYuan: Study design, interpretation of data, drafting of the manuscript, critical revision. JJZ, CGS, ZHZ, YYZ, QG: Acquisition, analysis and interpretation of data. FYang: Study concept and design, critical revision, study supervision. WJ: Study concept and design, critical revision, mobilisation of funding. All authors read and approved the final manuscript.

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References

[1] Misra UK, Kalita J. Seizures in encephalitis: predictors and outcome. Seizure 2009;18:583–7.
[2] Thakur KT, Motta M, Asemota AO, Kirsch HL, Benavides DR, Schneider EB, et al. Predictors of outcome in acute encephalitis. Neurology 2013;81:793–800.
[3] Liu X, Yan B, Wang R, Li C, Chen C, Zhou D, et al. Seizure outcomes in patients with anti-NMDAR encephalitis: a follow-up study. Epilepsia 2017;58:2104–11.
[4] Pillai SC, Mohammad SS, Hacohen Y, Tantsis E, Prelog K, Barnes EH, et al. Postencephalitic epilepsy and drug-resistant epilepsy after infectious and antibody-associated encephalitis in childhood: clinical and etiologic risk factors. Epilepsia 2016;57:e7–11.
[5] Yuan F, Jia R, Gao Q, Yang F, Yang X, Jiang Y, et al. Early predictors of drug-resistant epilepsy development after convulsive status epilepticus. Eur Neurol 2018;79:325–32.
[6] Zou X, Hong Z, Chen J, Zhou D. Is antiepileptic drug withdrawal status related to quality of life in seizure-free adult patients with epilepsy? Epilepsy Behav 2014;31:129–35.
[7] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus–report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56:1515–23.
[8] Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013;57:1114–28.
[9] Kalviainen R. Status epilepticus treatment guidelines. Epilepsia 2007;48(Suppl 8):99–102.
[10] Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol 2006;13:445–50.
[11] Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol 2010;17:348–55.
[12] Neurocritical Care Group from Chinese Medical Association's Neurology Chapter. Chinese expert consensus for monitoring and management of adult patients with convulsive status epilepticus. Chin J Neurol 2014;47:661–6.
[13] Gao Q, Ou-Yang TP, Sun XL, Yang F, Wu C, Kang T, et al. Prediction of functional outcome in patients with convulsive status epilepticus: the END-IT score. Crit Care 2016;20:46.
[14] Sutter R, Grize L, Fuhr P, Ruegg S, Marsch S. Acute-phase proteins and mortality in status epilepticus: a 5-year observational cohort study. Crit Care Med 2013;41:1526–33.
[15] Gunawardane N, Fields M. Acute symptomatic seizures and provoked seizures: to treat or not to treat? Curr Treat Options Neurol 2018;20:41.
[16] Vezzani A, Fujinami RS, White HS, Preux PM, Blumcke I, Sander JW, et al. Infections, inflammation and epilepsy. Acta Neuropathol 2016;131:211–34.
[17] Hesdorffer DC, Benn EK, Cascino GD, Hauser WA. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. Epilepsia 2009;50:1102–8.
[18] Bergey GK. Management of a first seizure. Continuum (Minneap Minn) 2016;22:38–50.
[19] Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391–404.
[20] Li W, Sun X, Yuan F, Gao Q, Ma Y, Jiang Y, et al. Diagnostic accuracy of cerebrospinal fluid procalcitonin in bacterial meningitis patients with empiric antibiotic pretreatment. J Clin Microbiol 2017;55:1193–204.
[21] Schwarz S, Bertram M, Schwab S, Andrassy K, Hacke W. Serum procalcitonin levels in bacterial and abacterial meningitis. Crit Care Med 2000;28:1828–32.
[22] Dagsdóttir HM, Sigurðardóttir B, Gottfreðsson M, Kristjánsson M, Löve A, Baldvinsdóttir GE, et al. Herpes simplex encephalitis in Iceland 1987-2011. Springerplus 2014;3:524.
[23] Singh TD, Fugate JE, Hocker S, Wijdicks EFM, Aksamit Jr AJ, Rabinstein AA. Predictors of outcome in HSV encephalitis. J Neurol 2016;263:277–89.
[24] Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–65.
[25] Tyler KL. Acute viral encephalitis. N Engl J Med 2018;379:557–66.
[26] van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. N Engl J Med 2006;354:44–53.
[27] Singh TD, Fugate JE, Rabinstein AA. The spectrum of acute encephalitis causes, management, and predictors of outcome. Neurology 2015;84:359–66.
[28] Chi X, Wang W, Huang C, Wu M, Zhang L, Li J, et al. Risk factors for mortality in patients with anti-NMDA receptor encephalitis. Acta Neurol Scand 2017;136:298–304.
[29] de Montmollin E, Demeret S, Brule N, Conrad M, Dailler F, Lerolle N, et al. Anti-N-methyl-d-aspartate receptor encephalitis in adult patients requiring intensive care. Am J Respir Crit Care Med 2017;195:491–9.
[30] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82.
[31] Bale Jr JF, Du Pasquier R. Relapse in herpes simplex virus encephalitis it's not just about the virus. Neurology 2015;85:1730–1.
[32] Cunha BA, Eisenstein LE, Wirkowski E, Klein NH, Johnson DH. West Nile encephalitis relapse presenting with abducens and facial nerve palsies. Am J Med 2006;119:e1–2.
[33] Wickstrom R, Fowler A, Cooray G, Karlsson-Parra A, Grillner P. Viral triggering of anti-NMDA receptor encephalitis in a child - an important cause for disease relapse. Eur J Paediatr Neurol 2014;18:543–6.
[34] Omi T, Kinoshita M, Nishikawa A, Tomioka T, Ohmori K, Fukada K, et al. Clinical relapse of anti-AMPAR encephalitis associated with recurrence of thymoma. Intern Med 2018;57:1011–3.
[35] Skoldenberg B, Aurelius E, Hjalmarsson A, Sabri F, Forsgren M, Andersson B, et al. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. J Neurol 2006;253:163–70.
[36] Hacohen Y, Deiva K, Pettingill P, Waters P, Siddiqui A, Chretien P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. Mov Disord 2014;29:90–6.
[37] Connolly MP, Goodwin E, Schey C, Zummo J. Toxoplasmic encephalitis relapse rates with pyrimethamine-based therapy: systematic review and meta-analysis. Pathog Glob Health 2017;111:31–44.
[38] Rossetti AO, Logroscino G, Bromfield EB. A clinical score for prognosis of status epilepticus in adults. Neurology 2006;66:1736–8.