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Prevalence and factors associated with seizures among patients with infective encephalitis

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ABSTRACT

Introduction: Seizures are a common and clinically significant complication of infective encephalitis, often associated with greater disease severity and poorer neurological outcomes. Identifying reliable clinical and diagnostic predictors of seizures is critical to improve early risk stratification and guide targeted management. However, regional data on the seizure prevalence and associated factors in encephalitis remain limited. This study aims to determine the prevalence, clinical characteristics, and risk factors associated with seizure occurrence in patients with infective encephalitis admitted to a tertiary care centre in Malaysia.

Materials and Methods: We conducted a retrospective observational study involving 173 patients diagnosed with infective encephalitis and admitted to a tertiary referral hospital. Data on demographics, clinical presentation, Glasgow Coma Scale (GCS) scores, electroencephalography (EEG), neuroimaging, and cerebrospinal fluid (CSF) parameters were extracted from medical records. Seizure occurrence and characteristics were analysed. Statistical analyses included univariate and multivariate logistic regression to identify independent predictors of seizures. Missing data for selected variables were imputed using median substitution based on the distribution of available data.

Results: Seizures were reported in 55.5% of patients (n=96), with generalised seizures being more common than focal. EEG abnormality emerged as the most significant independent risk factor for seizure occurrence (aOR 5.22, 95% CI 2.22–12.26, p <0.001). Altered behaviour (aOR 0.22, 95% CI 0.11-0.45, p < 0.001) and elevated CSF protein (OR 0.44, 95% CI 0.20–0.95, p = 0.036) were significantly associated with lower odds of seizures. Functional outcomes at discharge (assessed by Glasgow Outcome Scale), showed that higher seizure burden, particularly status epilepticus (p<0.001) and increased seizure frequency (p=0.008) was significantly associated with poorer recovery at discharge.

Conclusion: This study confirms the substantial clinical burden of seizures in infective encephalitis and highlights the need to prioritise systemic risk stratification in routine care. EEG abnormality is the strongest independent predictor of seizure risk and should be incorporated into early diagnostic evaluation for risk stratification. Early EEG monitoring, timely antiseizure management, and structured neurological assessment are critical to mitigate secondary brain injury and optimise outcomes.

KEYWORDS:
Infective encephalitis; seizures; risk factors; Malaysia

INTRODUCTION

Encephalitis, defined as inflammation of the brain parenchyma accompanied by neurologic dysfunction, arises from direct central nervous system (CNS) infection or immune-mediated mechanisms.[1,2] Globally, the incidence of clinically diagnosed encephalitis ranges from 3.5 to 7.4 cases per 100,000 population annually. The age-standardized incidence rate of encephalitis was found to be higher in low-middle regions, reaching 31.63/100,000 in 2019. The incidence of encephalitis was 5.23/100,000 in England compared to 185/100,000 in Nepal during an outbreak of Japanese encephalitis.[3,4] The aetiological spectrum is broad, encephalitis can be divided into infective and non-infective encephalitis including autoimmune disorders and paraneoplastic syndromes.[5,6] Differential diagnoses include metabolic encephalopathies, CNS neoplasms, and vasculitis, necessitating meticulous clinical and laboratory evaluation.[7]

The most common symptoms in encephalitis include acute or subacute mental state changes, fever, headache, focal neurological deficits, and seizures.[1,5] The consensus case definition incorporates altered mental status lasting ≥24 hours, accompanied by at least two of the following: fever ≥38°C within 72 hours of presentation, seizures not attributable to a known seizure disorder, new-onset focal neurological signs, cerebrospinal fluid (CSF) pleocytosis (white blood cell count ≥5/mm³), neuroimaging abnormalities, or electroencephalogram (EEG) findings consistent with encephalitis.[1]

Seizures represent a frequent and critical complication, reflecting severe neurological injury and often correlating

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with impaired consciousness, abnormal neuroimaging, and EEG changes.2,8 The International League Against Epilepsy (ILAE) defines acute symptomatic seizures as those occurring within seven days of a CNS insult.[9] Reported seizure incidence in encephalitis varies from 2% to 67%, depending on aetiology and study design.[2,10] In one clinical cohort, approximately one-third of encephalitis patients experienced seizures during hospitalisation.[11]

Seizure occurrence signals greater disease severity, complicates management and portends poorer outcomes, including prolonged hospitalisation, increased intensive care requirements, and an elevated risk of long-term sequelae such as post-encephalitic epilepsy (PEE).[2,8] Evidence suggests that patients who have had an acute seizure are more likely to develop chronic epilepsy. Longitudinal studies indicated that patients with acute seizures post-encephalitis have a substantially higher 20-year risk of developing epilepsy following viral encephalitis (22%) compared to those without seizures (10%).10 Development of PEE necessitates prolonged antiseizure therapy and is associated with diminished functional independence and quality of life.[10,12,13]

Despite advancements in diagnostics and therapeutics, encephalitis remains a leading cause of morbidity and mortality worldwide, with fatality rates ranging from 5.6% to 39.3%.[6] Persistent neurological impairments, including memory loss, behavioural disturbances, fatigue, and recurrent seizures, contribute to long-term disability.[13] Notably, the epidemiology and clinical profile of seizures in encephalitis within South East Asia remain insufficiently characterised. This region harbours distinct viral aetiologies, such as Japanese encephalitis virus (JEV), which is the predominant cause of encephalitis.[14] However, comprehensive, harmonized data on seizure prevalence, risk factors, and outcomes in encephalitis across South East Asia are scarce, partly due to heterogeneous diagnostic capabilities and limited prospective studies. This paucity of data hampers effective risk stratification, targeted management and public health interventions. Addressing this critical knowledge gap, our study aims to systematically evaluate the prevalence, clinical characteristics and correlates of seizure occurrence in patients with infective encephalitis admitted to a tertiary health care centre in South East Asia.

MATERIALS AND METHODS

Study design and population

This was a single-centre, retrospective study, conducted at Hospital Canselor Tuanku Muhriz (HCTM), a tertiary academic hospital in Malaysia. The study population consisted of adult patients (aged 18 years or older) admitted with a clinical diagnosis of infective encephalitis between 1st January 2016 and 31st May 2025. Ethical approval was obtained through the local Ethics and Research Board (JEP-2023-519).

The diagnosis of infective encephalitis was based on clinical, laboratory, and radiological criteria, following the International Encephalitis Consortium definition: altered mental status lasting ≥24 hours without an alternative cause, accompanied by at least two of the following—fever ≥38°C within 72 hours of presentation, seizures not attributable to a pre-existing seizure disorder, new-onset focal neurological signs, CSF pleocytosis (white cell count ≥5/mm³), brain imaging suggestive of encephalitis, or EEG abnormalities consistent with encephalitis.[1] Seizures were classified as acute symptomatic seizures if they occurred within seven days of encephalitis onset, following the International League Against Epilepsy (ILAE) definition.[9]

Patients with autoimmune encephalitis, prior stroke, traumatic brain injury, brain tumour, previous neurosurgery, or other chronic neurological disorders unrelated to encephalitis were excluded.

Data collection

Eligible patients were identified through hospital medical records and infectious disease registries. With assistance from the medical records department, relevant data were manually extracted and entered into a data collection form. Variables collected included demographic details (age, sex, ethnicity), clinical characteristics (fever, headache, altered behaviour, Glasgow Coma Scale [GCS] score, and seizure occurrence), comorbidities (e.g., diabetes mellitus, hypertension, tuberculosis), CSF parameters (protein, glucose, pleocytosis, and culture results), EEG and neuroimaging findings, seizure type and frequency, and antiseizure medication use. Patients were subsequently categorised into two groups based on the presence or absence of seizures.

Sample size

Sample size estimation was performed for both prevalence and comparative analyses.

$$n = \left[\frac{Z}{\Delta}\right]^2 p(1-p)$$

n : required sample size
p : prevalence from previous study (Annegers et al)(10)
Z : 1.96 for 95% confidence interval
Δ : absolute precision = 0.05

Assuming p = 0.068 (6.8% prevalence from Annegers et al(10) with Z = 1.96 (95% CI) and Δ = 0.05, the calculated sample size was 97 patients

For comparative analysis of risk factors, the sample size was calculated using the formula for two-proportion described by Rosner's method.(15)

$$N = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \, \delta^2}{d^2}$$

N : sample size per group
Zα/2 : 1.96 for 95% confidence
Zβ : 0.84 for 80% power
δ : standard deviation
d : clinically meaningful difference between group means

Based on data from Granerod et al.,[16] which identified 203 patients with encephalitis, with 42% attributed to infectious causes and 21% to immune-mediated aetiologies, a minimum of 73 patients per group was required. Allowing for a 10% dropout rate, the final estimated sample size was 81 per group, totalling 162 patients.

Statistical Analysis
Data were analysed using 'Statistical Product and Service Solution' (SPSS), Version 30. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as means ± standard deviation or medians (25th, 75th percentile) depending on normality of distribution.

Statistical analyses included both descriptive and inferential methods. Univariate analyses were performed to describe the profiling of the samples and bivariate analyses were performed to assess associations between independent variables and seizure occurrence using Pearson's Chi square. Variables that were statistically significant in the bivariate analysis, as well as those considered clinically relevant, were included in the multivariate logistic regression model to identify independent predictors of seizure occurrence after adjusting for confounding factors. Results from binary logistic regression are presented as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI) and p-values. Statistical significance was set at $p < 0.05$.

Missing Data Management:
Missing data were identified in 8.7% of CSF parameters, 5.9% of EEG data, and 1.2% of neuroimaging findings. To address missing data and minimise potential bias, imputation was performed using the median for continuous variables (CSF protein = 489 mg/dL; CSF glucose = 3.75 mmol/L) and the most frequent category for categorical variables (CSF culture = "no growth," EEG = "normal," neuroimaging = "normal"). This single-imputation approach was chosen to maintain the overall distribution of variables for analysis, provided that the proportion of missing data did not exceed 10% for each variable.

RESULTS

Descriptive Statistics
205 patients with presentation of encephalitis were screened for this study. Eventually, 173 participants diagnosed with infective encephalitis were recruited in the study. The mean age was 46.8 years (SD ± 20) with a slight male predominance (n=96, 55.5%). Seizures were reported in 96 participants (55.4%), predominantly affecting young adults aged 18–44 years.

Hypertension (n=54, 31.2%) and diabetes mellitus (n=45, 26.0%) were the most frequently reported comorbidities. Both conditions were slightly more prevalent in the non-seizure group. No significant differences were observed between groups for other comorbidities, including dyslipidaemia, ischaemic heart disease, tuberculosis, HIV, or psychiatric disorders.

Fever was the most frequently reported presenting symptom (n=108, 62.4%), followed by altered behaviour (n=90, 52%) and headache (n=48, 27.7%). Fever was slightly more common among patients with seizures (n=57, 59.4%), whereas altered behaviour was predominantly observed in those without seizures (n=54, 70.1%). Lethargy and focal motor weakness were infrequent across the cohort. The median GCS score at presentation was 14 (11,15). The majority of patients (n=159, 91.9%) presented with GCS 10–15, while a lower GCS of 3–9 was seen more frequent in the seizure group (n= 12, 12.5%) than in the non-seizure group (n=2, 2.6%).

CSF analysis was available for 158 patients. Positive CSF culture growth was detected in 40 cases (23.1%), with viral pathogens being the most frequently isolated (20, 11.6%), followed by bacterial (n=5, 2.9%), Toxoplasma (n=3, 1.7%) and Cryptococcal organisms (2, 1.2%). Biochemical abnormalities such as elevated protein levels >400 mg/L was identified in 95 cases (54.9%), and low glucose levels <2.22 mmol/L in 18 cases (10.4%). Elevated CSF protein was more frequent in the seizures group (n=48, 50.0%), while low CSF glucose levels were slightly more prevalent in the non-seizure group (n=9, 11.7% vs. n=9, 9.4%). CSF pleocytosis (WBC ≥5/mm³) was infrequent (n=9, 5.2%) and showed no significant difference between the two groups.

Abnormal neuroimaging was noted in 86 patients (49.7%), more commonly among those with seizures (n=52, 54.2%). EEG was performed in 163 patients, revealing abnormal findings in 109 (63.0%), significantly more frequent in the seizure group (n=71, 74.0% vs. n=38, 49.4%). Among the 96 seizure patients, generalized seizures were more common (n=70, 72.9%) compared to focal seizures (n=26, 27.1%). Status epilepticus occurred in 26 patients (27.1%). Seizure onset was typically early in the clinical course, with a median time of 1 day (0,2) following initial presentation of encephalitis symptoms. Most patients experienced infrequent seizures; only 13 (7.3%) reported five or more episodes per month.

Antiseizure medications were prescribed in 73 seizure patients (76.0%), most of whom received monotherapy (n=53, 55.2%), while 20.8% received polytherapy. The overall treatment burden was low, with a median number of antiseizure medications of 0 (0, 1).

Functional outcomes of patients at discharge were assessed using Glasgow Outcome Score (GOS), score (Table II). Majority of patients (n = 130, 75.1%) achieved good recovery, while 15 (8.7%) had severe disability, 12 (6.9%) had moderate disability, 2 (1.2%) remained in a neurovegetative state, and 14 (8.1%) died. The distribution of GOS score did not differ significantly between seizure and non-seizure groups ($p = 0.165$).

Patients who developed status epilepticus was significantly associated with poorer outcomes ($p < 0.001$), including higher rates of death (n=4/26, 15.4%) and severe disability (n= 7/26, 26.9%) compared with those without status epilepticus. Similarly, increasing seizure frequency was significantly associated with worse functional outcomes at discharge ($p = 0.008$; linear-by-linear association $p = 0.048$). In contrast, seizure type (focal vs. generalised) showed no significant association with GOS score ($p = 0.287$). In summary, while seizure occurrence alone did not significantly influence overall outcome, the occurrence of status epilepticus and higher seizure frequency were strongly associated with poorer functional outcomes.

Table I: Sociodemographic, clinical characteristics and investigation parameters of study participants with seizure presentation

Demographic/Clinical characteristics	Total (N=173)	No seizure (N=77)	With seizure (N=96)	p-value
Age group, n (%)				0.500 [a]
18 – 44	89 (51.4)	37 (48.1)	52 (54.2)	
45 – 64	40 (23.1)	21 (27.3)	19 (19.8)	
65 and above	44 (25.4)	19 (24.7)	25 (26.0)	
Gender, n (%)				0.823 [a]
Male	96 (55.5)	42 (54.5)	54 (56.3)	
Female	77 (44.5)	35 (45.5)	42 (43.6)	
Race, n (%)				0.786 [a]
Malay	96 (55.5)	41 (53.2)	55 (57.3)	
Chinese	55 (31.8)	27 (35.1)	28 (29.2)	
Indian	13 (7.5)	6 (7.8)	7 (7.3)	
Others	9 (5.2)	3 (3.9)	6 (6.3)	
Concomitant diseases, n (%)				
Hypertension				0.328 [a]
Yes	54 (31.2)	27 (35.1)	27 (28.1)	
No	119 (68.8)	50 (64.9)	69 (71.9)	
Diabetes mellitus				0.735 [a]
Yes	45 (26.0)	21 (27.3)	24 (25.0)	
No	128 (74.0)	56 (72.7)	72 (75.0)	
Dyslipidaemia				0.887 [a]
Yes	30 (17.3)	13 (16.9)	17 (17.7)	
No	143 (82.7)	64 (83.1)	79 (82.3)	
Ischemic heart disease				0.488 [a]
Yes	9 (5.2)	3 (3.9)	6 (6.3)	
No	164 (94.8)	74 (96.1)	90 (93.8)	
Tuberculosis infection				0.256 [a]
Yes	8 (4.6)	2 (2.6)	6 (6.3)	
No	165 (95.4)	75 (97.4)	90 (93.8)	
HIV disease				0.575 [a]
Yes	6 (3.5)	2 (2.6)	4 (4.2)	
No	167 (96.5)	75 (97.4)	92 (95.8)	
Psychiatric illness				0.613 [a]
Yes	4 (2.3)	1 (1.3)	3 (3.1)	
No	169 (97.7)	76 (98.7)	93 (96.9)	
Symptoms on presentation				
Fever				0.355 [a]
Yes	108 (62.4)	51 (66.2)	57 (59.4)	
No	65 (37.6)	26 (33.8)	39 (40.6)	
Lethargy				0.081 [a]
Yes	47 (27.2)	26 (33.8)	21 (21.9)	
No	126 (72.8)	51 (66.2)	75 (78.1)	
Headache				0.828 [a]
Yes	48 (27.7)	22 (28.6)	26 (27.1)	
No	125 (72.3)	55 (71.4)	70 (72.9)	
Altered behaviour				<0.01 [a]
Yes	90 (52.0)	54 (70.1)	36 (37.5)	
No	83 (48.0)	23 (29.9)	60 (62.5)	
Weakness				0.492 [a]
Yes	7 (4.0)	4 (5.2)	3 (3.1)	
No	166 (96.0)	73 (94.8)	93 (96.9)	
GCS on presentation, n (%)				0.021 [a]
GCS 3-9	14 (8.1)	2 (2.6)	12 (12.5)	
GCS 10-15	159 (91.9)	75 (97.4)	84 (87.5)	
CSF culture findings, n (%)				0.864 [a]
Positive growth	40 (23.1)	21 (27.3)	19 (19.8)	
No growth	118 (68.2)	49 (63.6)	69 (71.9)	
Not available	15 (8.7%)	7 (9.1)	8 (8.3)	
CSF culture growth type, n (%)				0.939 [a]
Bacterial	5 (2.9)	3 (3.9)	2 (2.1)	
Viral	20 (11.6)	9 (11.7)	11 (11.5)	
Fungal/Cryptococcal	2 (1.2)	1 (1.3)	1 (1.0)	
Parasitic/Toxoplasma	3 (1.7)	2 (2.6)	1 (1.0)	
No growth	128 (74.0)	55 (71.4)	73 (76.0)	
Not available	15 (8.7)	7 (9.1)	8 (8.3)	

Table I: Sociodemographic, clinical characteristics and investigation parameters of study participants with seizure presentation

Demographic/Clinical characteristics	Total (N=173)	No seizure (N=77)	With seizure (N=96)	p-value
CSF investigation findings, n (%)				
Low Glucose levels (<2.22 mmol/L)				0.862 [a]
Yes	18 (10.4)	9 (11.7)	9 (9.4)	
No	140 (80.9)	61 (79.2)	79 (82.3)	
Not available	15 (8.7)	7 (9.1)	8 (8.3)	
Elevated Protein levels (>400 mg/dL)				0.271 [a]
Yes	95 (54.9)	47 (61.0)	48 (50.0)	
No	63 (36.4)	23 (29.9)	40 (41.7)	
Not available	15 (8.7)	7 (9.1)	8 (8.3)	
Cell count/ Pleocytosis (WBC ≥5 cells/μ)				0.271 [a]
Present	9 (5.2)	6 (7.8)	3 (3.1)	
Absent	149 (86.1)	64 (83.1)	85 (88.3)	
Not available	15 (8.7)	7 (9.1)	8 (8.3)	
Neuroimaging findings, n (%)				0.425 [a]
Abnormal	86 (49.7)	34 (44.2)	52 (54.2)	
Normal	85 (49.1)	42 (54.5)	43 (44.8)	
Not available	2 (1.2)	1 (1.3)	1 (1.0)	
EEG findings, n (%)				0.003 [a]
Abnormal	109 (63.0)	38 (49.4)	71 (74.0)	
Normal	54 (31.2)	32 (41.6)	22 (22.9)	
Not available	10 (5.8)	7 (9.1)	3 (3.1)	
Type of seizure, n (%)				-
Focal seizure	26 (15.0)	0 (0.0)	26 (27.1)	
Generalized seizure	70 (40.5)	0 (0.0)	70 (72.9)	
No seizure	77 (44.5)	77 (100)	0 (0.0)	
Seizure frequency/month, n (%)				-
No seizure	77 (44.5)	0 (0.0)	0 (0.0)	
1 -2 seizure	52 (30.1)	0 (0.0)	0 (0.0)	
3 -4 seizure	31 (17.9)	0 (0.0)	0 (0.0)	
5 or more seizure	13 (7.3)	0 (0.0)	0 (0.0)	
Status Epilepticus, n (%)				-
Yes	26 (15.0)	0 (0.0)	26 (27.1)	
No	147 (85.0)	77 (100)	70 (72.9)	
Medication status, n (%)				-
No antiseizure medication	100 (57.8)	77 (100)	23 (24.0)	
Single antiseizure medication	53 (30.6)	0 (0.0)	53 (55.2)	
2 or more antiseizure medication	20 (11.6)	0 (0.0)	20 (20.8)	
		Mean ± SD (95% CI)		
Age (years)		46.80 ± 20.0 (43.8 – 49.8)		
		Median (Percentile 25th, 75th)		
GCS on presentation		14 (11, 15)		
Onset of seizure after encephalitis presentation		1 (0, 2)		
Seizure frequency within 1 month		1 (0, 3)		
Number of anti-seizure medications		0 (0,1)		

[a] Chi-square test

Statistically significant results ($p < 0.05$) are indicated in bold.

Associated factors and Independent Predictors of Seizure risk in infective encephalitis

Simple binary logistic regression was performed to determine the association between clinical and diagnostic variables and the occurrence of seizures among patients with infective encephalitis (Table III). Bivariate analysis showed that altered behaviour ($p<0.001$), low GCS on presentation ($p=0.024$), and abnormal EEG ($p=0.001$) findings were significantly associated with seizure occurrence. Other parameters, including age, gender, comorbidities, fever on presentation, low CSF glucose levels, elevated CSF protein and the presence of CSF pleocytosis, were not significantly associated with seizure occurrence.

A multivariate binary logistic regression was performed to identify independent risk factors associated with seizure occurrence in infective encephalitis (Table IV). Variables included in the model were those found to be statistically significant in the bivariate analysis and clinically relevant factors identified from prior literature of encephalitis, to ensure a robust and comprehensive model.

The overall multivariate model was statistically significant, $\chi^2(10, N=173) = 45.987$, $p < 0.001$, indicating that the set of predictors reliably distinguished between patients with and without seizures. The model explained 23.3% to 31.2% of the variance (Cox & Snell R^2, Nagelkerke R^2) and correctly classified 55.5% of cases. Goodness-of-fit was confirmed by a

Table II: Association between seizure characteristics and Glasgow Outcome Score (GOS) among patients with infective encephalitis

Glasgow Outcome scale (GOS) Score	[1] Death	[2] Neuro-vegetative state	[3] Severe disability	[4] Moderated disability	[5] Good recovery	Total	p-value
Seizure							0.165
Yes	9 (9.4)	2 (2.1)	11 (11.5)	4 (4.2)	70 (72.9)	96 (100)	
No	5 (6.5)	0 (0.0)	4 (5.2)	8 (10.4)	60 (77.9)	77 (100)	
Type of Seizure							0.287
No seizure	5 (6.5)	0 (0)	4 (5.2)	8 (10.4)	60 (77.9)	77 (100)	
Focal	1 (3.8)	1 (3.8)	2 (7.7)	1 (3.8)	21 (80.8)	26 (100)	
Generalized	8 (11.4)	1 (1.4)	9 (12.9)	3 (4.3)	49 (70.0)	70 (100)	
Status Epilepticus							<0.001
Yes	4 (15.4)	2 (7.7)	7 (27.0)	1 (3.8)	12 (46.2)	26 (100)	
No	10 (6.8)	0 (0)	8 (5.4)	11 (7.5)	118 (80.3)	147 (100)	
Seizure frequency/ month							0.008
No seizure	5 (6.5)	0 (0)	4 (5.2)	8 (10.4)	60 (77.9)	77 (100)	
1 -2 seizure	5 (9.6)	0 (0)	4 (7.7)	3 (5.8)	40 (76.9)	52 (100)	
3 -4 seizure	3 (9.7)	1 (3.2)	2 (6.5)	1 (3.2)	24 (77.4)	31 (100)	
5 or more	1 (7.7)	1 (7.7)	5 (38.5)	0 (0)	6 (56.1)	13 (100)	

Significant p value <0.05

Table III: Simple logistic regression testing association factors for seizure occurrence in infective encephalitis

Variable	Crude OR (cOR)	95% CI	p-value
CSF protein			
Normal	Ref	0.295 – 1.062	0.076
High (>400 mg/L)	0.560		
EEG			
Normal	Ref	1.540 – 5.518	0.001
Abnormal	2.915		
GCS on presentation			
10–15	Ref	1.139 – 6.481	0.024
3–9	0.024		
Brain imaging			
Normal	Ref	0.818 – 2.731	0.191
Abnormal	1.495		

cOR: Crude Odds ratio
95% CI – 95% Confidence Interval
Significant p value <0.05

Table IV: Multivariate Binary logistic regression in predicting seizures in patients with infective encephalitis

Variable	B	SE	Wald	df	p	aOR	95% C.I. for OR	
							LL	UL
Age (years)								
18–44			1.844	2	0.398			
45–64	-0.665	0.500	1.766	1	0.184	0.514	0.193	1.371
>65	-0.455	0.511	0.792	1	0.374	0.635	0.233	1.728
Comorbidities								
Yes	-0.206	0.432	0.228	1	0.633	0.814	0.349	1.896
Fever	-0.025	0.382	0.004	1	0.947	0.975	0.461	2.063
Lethargy	-0.476	0.409	1.353	1	0.245	0.621	0.279	1.386
Altered behaviour	-1.524	0.373	16.731	1	<0.001	0.218	0.105	0.452
GCS on presentation								
10 -15	Ref							
3 - 9	0.670	0.522	1.650	1	0.199	1.955	0.703	5.435
Elevated CSF protein								
(>400 mg/L)	-0.828	0.395	4.393	1	0.036	0.437	0.201	0.948
Brain imaging								
Abnormal	0.172	0.382	0.202	1	0.653	1.187	0.562	2.510
EEG abnormality	1.653	0.435	14.399	1	<0.001	5.220	2.223	12.257
Constant	0.876	0.478	3.348	1	0.067	2.400	-	-

B – Regression Coefficient
S.E – Standard Error
Wald – Chi Square statistics
df – degree of freedom
p-value – Significant p value <0.05 (in bold)
aOR– Adjusted Odds Ratio
95% CI – 95% Confidence Interval for adjusted odd ratio, LL - Lower Limit, UL- Upper Limit

non-significant Hosmer–Lemeshow test, $\chi^2(8, N=173) = 6.198$, $p = 0.625$, suggesting an adequate model fit. The results are reported as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI) and p-values.

From the multivariate logistic regression analysis, altered behaviour, elevated CSF protein and abnormal EEG findings remained significantly associated with seizure occurrence after adjusting for potential confounders.

Abnormal EEG findings were strongly associated with an increased odds of seizures risk (adjusted OR = 5.220, 95% CI = 2.22–12.26, $p < 0.001$). this suggest that patient with abnormal EEG are approximately 5.2 times higher risk of developing seizures than those without.

In contrast, patients presenting with altered behaviour had significantly lower odds of seizures (adjusted OR = 0.218, 95% CI = 0.105–0.452, $p < 0.001$). Similarly, those with elevated CSF protein levels (>400 mg/L) showed a lower likelihood of seizure occurrence (adjusted OR = 0.437, 95% CI = 0.201–0.948, $p = 0.036$). Although reduced GCS score was associated with seizures occurrence on unadjusted univariate analysis, this association lost statistical significance after adjustment for other confounders in the multivariate model.

Other variables, including age, presence of comorbidities, lethargy, fever and abnormal brain imaging were not independently associated with seizure occurrence ($p > 0.05$ for all).

In summary, abnormal EEG findings were significantly associated with increase odds of abnormal seizure risk in infective encephalitis, while altered behaviour, low GCS on presentation and elevated CSF protein levels were more commonly observed in patients without seizures. Occurrence of status epilepticus and higher seizure frequency were strongly associated with poorer functional outcomes. No significant associations were found with demographic characteristics, comorbidities, or most CSF and neuroimaging parameters.

DISCUSSION

This study provides valuable insights into the prevalence and factors associated with acute seizure development in patients diagnosed with infective encephalitis in a tertiary care setting in Malaysia.

The prevalence of seizures observed in our study was 55.4%, highlighting the substantial neurological morbidity associated with encephalitis and reaffirming the role of seizures as a common and clinically significant complication in this patient population. The seizure prevalence reported in our cohort is notably higher compared to existing broader literature, where seizure rates were reported ranging from 2% to 67%, depending on differences in study design, case definitions, and underlying etiologies.[2,10] Similarly, another study focusing specifically on confirmed infectious encephalitis reported seizure rates ranging from 33% to 40%.[1] In comparison, comparable seizure rates have been observed in studies conducted within the Asian population, including, a Japanese study that reported a prevalence of 48% among patients with viral encephalitis.[17] The slightly higher prevalence in our cohort, may be attributed to the tertiary referral nature of our study centre, where more severe and neurologically complicated cases are managed. Furthermore, the relatively high proportion of patients with status epilepticus (27.1%), along with the availability of routine EEG monitoring likely contributed to improved detection and classification of seizure activity.

In addition to determining seizure prevalence, this study systematically evaluated sociodemographic profiles and clinical characteristics to identify potential risk factors and predictive markers for seizure occurrence in patients with infective encephalitis. Neither gender nor ethnicity demonstrated a significant association with seizure development, a finding consistent with prior studies.[2,6] Although isolated reports have suggested that younger age may be a potential risk factor for seizures in encephalitis[6], this was not supported by multicentre data [2], nor was it observed in our study. Similarly, comorbidities such as hypertension and diabetes mellitus did not significantly influence seizure risk —a finding that has not been previously reported in the encephalitis literature, where systemic comorbidities remain largely underexplored. Most existing evidence come from chronic epilepsy cohorts, where these conditions are more prevalent among them.[18,19] The absence of such associations in acute infective encephalitis may reflect fundamental differences in seizure pathophysiology between acute neuroinflammatory processes and chronic epileptic syndromes.

Although lethargy and behavioural changes are frequent clinical features in encephalitis, their predictive value for seizures remains inconsistent. In our study, altered behaviour was significantly associated with reduced odds of seizures, consistent with previous reports, where behavioural disturbances were more frequently observed among non-seizure patients with encephalitis.[4] This suggests that, despite their common occurrence, these symptoms may not serve as independent predictors of seizure risk in encephalitis. A plausible explanation for this discrepancy lies in the timing of clinical assessments. As highlighted in prior research, postictal evaluations, especially in retrospective or non-seizure-focused studies—may obscure or under-represent behavioural abnormalities, leading to inconsistent associations with seizure risk.[2,20]

Reduced levels of consciousness, as assessed by the GCS have been consistently linked to an increased risk of seizures across multiple studies.[2,6,13] Although our study initially demonstrated a link between lower GCS and seizure occurrence in the unadjusted analysis, this association lost significance after adjustment for confounding factors. Collectively, these findings indicate that the relationship between reduced GCS and seizure occurrence may be mediated by other clinical or diagnostic variables, such as EEG abnormalities, suggesting that depressed consciousness reflects the extent and severity of encephalitic injury rather than a direct increase in seizure risk. There are various mechanisms which contribute to the seizure risk in patients with encephalitis, including neuroinflammation, activation

of the innate and adaptive immunity, dysregulation of microglial activity and cytokine production. The epileptogenic frontotemporal area is typically affected in Herpes simplex encephalitis, which affects the GCS state. These findings highlight the importance of distinguishing seizure-specific predictors from nonspecific encephalopathic features in the context of infective encephalitis.[21]

Among the CSF parameters, only elevated CSF protein levels were significantly associated with reduced odds of seizure occurrence, while low glucose and pleocytosis did not demonstrate a significant association with seizure risk in our study. These findings are consistent with multiple prior studies.[22–25] This likely reflects the multifactorial pathophysiology of encephalitis, which involves complex immune-mediated mechanisms such as blood–brain barrier disruption, cytokine-induced neuroinflammation, and neuronal hyperexcitability [26–28], none of which are fully captured by conventional CSF biochemical analysis.[20] For instance, elevated CSF protein may indicate neuroinflammation, but it does not necessarily reflect focal neuronal injury or excitability that could precipitate seizures. Although these CSF abnormalities remain fundamental in diagnosing encephalitis and determining its aetiology, their utility in stratifying seizure risk appears limited. Therefore, while CSF analysis remains indispensable for diagnostic purposes, it should not be relied upon as a standalone tool for predicting seizure risk in encephalitis.

Neuroimaging aids in the diagnosis of encephalitis by detecting structural abnormalities such as cerebral oedema, focal lesions and haemorrhagic changes.[29,30] Specific radiological patterns such as bilateral temporal lobe involvement and extensive cortical lesions have been linked to worse neurological outcomes and increased morbidity.[31] Despite its diagnostic value, our study did not demonstrate a statistically significant association between radiological abnormalities and seizure occurrence. This observation is supported by prior studies indicating that conventional imaging techniques may lack the sensitivity to detect transient or subtle electrophysiological disruptions associated with seizures.[2,32] Moreover, variability in imaging techniques, the timing of scans relative to seizure onset, and the presence of subclinical seizures may contribute to the absence of a detectable correlation.

EEG is a well-established diagnostic and prognostic modality in encephalitis, facilitating the detection of both clinical and subclinical seizure activity.[33] Characteristic EEG patterns, particularly lateralized periodic discharges (LPDs), have been strongly linked to higher seizure risk and worse clinical outcomes.[34-36] In our study, EEG abnormality emerged as the strongest independent predictor of seizures. Notably, 49.4% of EEG abnormalities were observed in patients without clinically apparent seizures, suggesting the presence of subclinical or non-convulsive seizure activity. The mechanisms of epileptogenesis include increased blood-brain barrier permeability, direct neuronal damage and ion channels modification, which ultimately lead to altered neuronal excitability and seizure generation. These results are consistent with previous works,[33,37–39] which emphasized the prognostic utility of EEG in predicting seizure risk and informing early therapeutic interventions.

Our study strengthens prior evidence that seizure burden, particularly status epilepticus and increase seizure frequency has a decisive impact on functional outcome, with affected patients demonstrating markedly poorer recovery at discharge. Consistent with earlier studies,[20] we found that prolonged or recurrent seizures were associated with lower GOS scores, reflecting the role of sustained cortical hyperexcitability in driving neurological decline. Although long-term outcomes were not assessed, the observation that most patients achieved seizure control with monotherapy suggests that early recognition and targeted antiseizure therapy may help mitigate secondary brain injury and support better functional recovery. Collectively, these findings highlight the importance of early EEG monitoring and prompt antiseizure management to improve functional recovery in infective encephalitis.

Overall, our study findings highlight the multifactorial nature of seizure pathophysiology in infective encephalitis. EEG abnormalities directly reflect cortical hyperexcitability and remain a robust clinical indicator of seizure susceptibility, whereas altered behaviour and elevated CSF protein levels represent broader encephalopathic processes that are not specific to seizure generation. Furthermore, seizure burden, particularly status epilepticus and high-frequency seizures has a more profound impact on neurological outcomes. These observations underscore the need for early EEG monitoring and clinical stratification based on neurological presentation to improve seizure risk prediction and enable more targeted management in patients with encephalitis. Furthermore, the observed link between early seizures and poorer outcomes further supports the need for timely recognition and intervention.

LIMITATIONS

The single-centre, retrospective design of this study limits generalisability and precludes causal inference. There is a potential for selection or information bias. Variability in EEG and CSF availability may have influenced some associations, while reliance on clinician judgement for clinical features such as altered behaviour introduces subjectivity. The absence of long-term follow-up further restricts conclusions regarding seizure recurrence and functional recovery. Future prospective, multi-centre studies with standardised protocols are needed to validate these findings.

CONCLUSION

Seizures are a common and clinically significant complication of infective encephalitis, frequently associated with increased morbidity, prolonged hospitalization, and an elevated risk of post-encephalitic epilepsy. In this cohort, seizures occurred in more than half of affected patients, underscoring their substantial clinical burden and the importance of timely recognition and management, both in the acute phase and in shaping long-term neurological outcomes.

Occurrence of status epilepticus and higher seizure frequency were strongly associated with poorer functional outcomes. This study identified EEG abnormalities as the most consistent and clinically relevant predictor of seizure

occurrence. These findings emphasise the value of incorporating early EEG monitoring into standard evaluation protocols for patients with infective encephalitis. Such measures enable the timely identification of high-risk individuals, facilitate early targeted interventions, and may ultimately reduce seizure burden while limiting secondary neuronal injury.

Conversely, CSF parameters, neuroimaging abnormalities, and behavioural changes did not demonstrate a significant increased seizure risk, highlighting the limitations of relying solely on structural or biochemical markers. The heterogeneity of clinical presentations and diagnostic findings further supports the need for an integrative approach, where functional and electrophysiological assessments are prioritised over isolated diagnostic parameters.

Taken together, these results contribute to a better understanding of the early clinical trajectory of seizure development in infective encephalitis and provide a foundation for improving clinical decision-making in the acute phase. Future research should prioritise prospective, multicentre validation across diverse populations and explore the integration of immunological and molecular biomarkers to refine prognostication and guide the development of precision-based seizure risk stratification models in encephalitis.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

INFORMED CONSENT STATEMENT

Patient consent was waived due to it being a retrospective study spanning across 9 years and de-identification before data analysis.

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