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PREDICTORS OF POOR OUTCOMES IN STATUS EPILEPTICUS: INSIGHTS FROM A UNIVERSITY HOSPITAL IN SAUDI ARABIA

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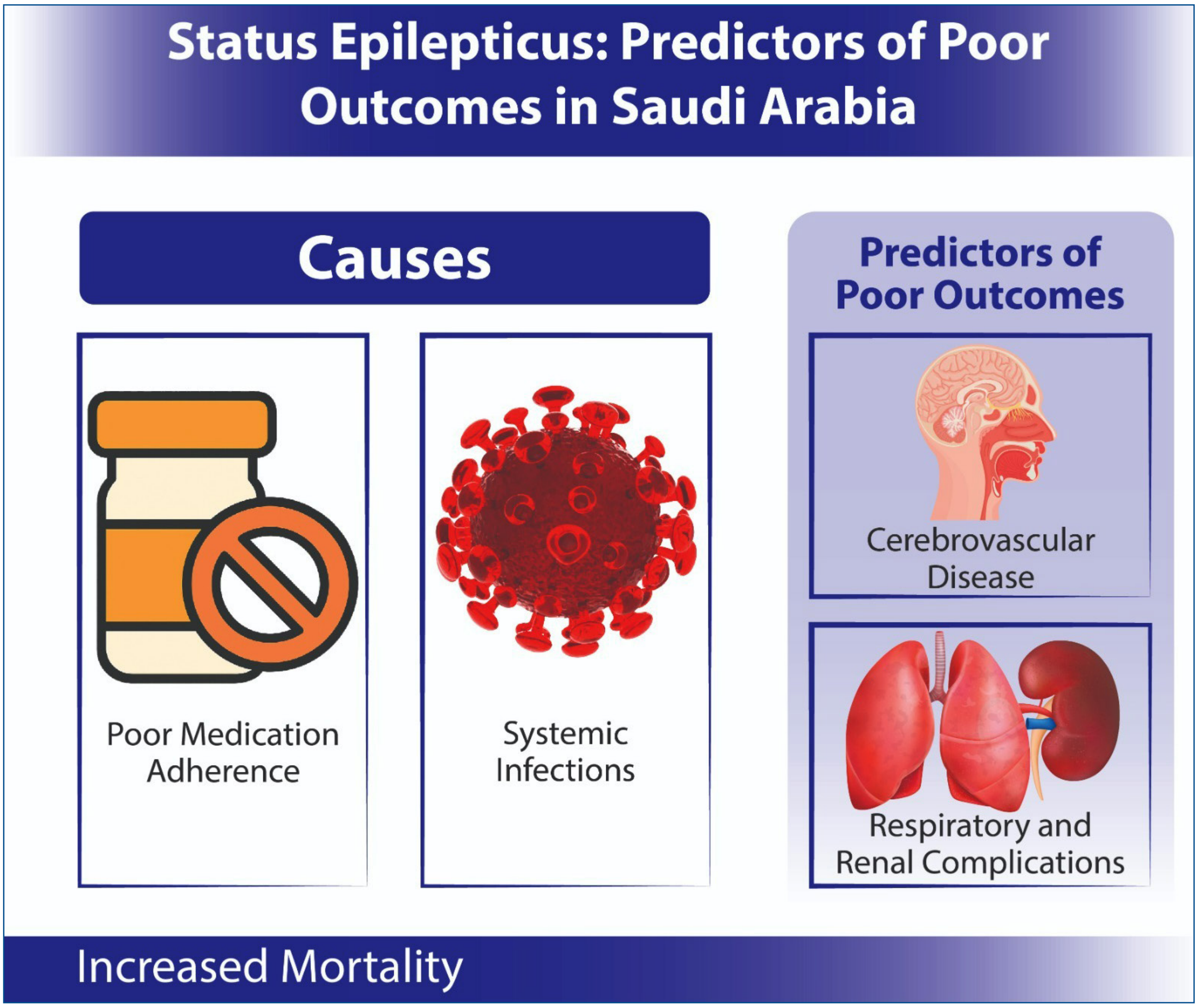
ABSTRACT – ***Objective:*** Status epilepticus (SE) is a life-threatening neurological emergency. However, studies on the prognostic factors of adult patients with SE in the Middle East remain lacking. Therefore, the present study aimed to analyze the clinical presentation, causes, and complications of SE and determine predictors of poor outcomes in patients treated in a tertiary care university hospital in Saudi Arabia.

Materials and Methods: This retrospective cohort study was conducted in the Department of Medicine, Neurology Division, College of Medicine, King Saud University, Riyadh, Saudi Arabia. This study recruited 38 patients aged 14 years or older who met the diagnostic criteria for SE. The median age was 30, and males accounted for 60.5% of cases. The outcomes were assessed using the Glasgow Outcome Scale (GOS).

Results: A history of epilepsy was present among 78.9% of patients; generalized seizures were observed in 89.5%, and focal seizures were observed in 10.59%. The primary complications included respiratory problems (36.89%) and acute kidney injury (23.7%). Antiepileptic drug reduction or withdrawal was the most common etiology in patients with preexisting epilepsy. Systemic infection (42.1%) was the most common cause in the general population, followed by withdrawal or reduction of anti-epileptic drugs (39.5%) and cerebrovascular disease (23.7%). Overall, 36.8% of patients experienced poor outcomes.

Conclusions: It was concluded that, overall, one-third of patients experienced poor outcomes. The mortality rate was 18.4%. The refractory SE, caused by cerebrovascular disease and respiratory/renal complications, was identified as a significant predictor of poor outcomes. This study highlights poor medication adherence and systemic infections as the primary causes of SE in Saudi Arabia. Refractory SE, respiratory complications, acute kidney injury, and SE due to cerebrovascular disease emerged as key predictors of poor outcomes, emphasizing the importance of addressing the underlying causes and the early recognition and management of complications.

KEYWORDS: Predictors, Clinical outcomes, Status epilepticus, Epilepsy.



Graphical Abstract. Predictors of poor outcomes of status epilepticus in Saudi Arabia.

INTRODUCTION

Status epilepticus (SE) is a life-threatening neurological emergency with high morbidity and mortality[1]. The prevalence of SE varies between 1.29 and 73.7/100,000 in adults[2]. The etiology of SE also shows significant variation between different populations and age groups[3], with 54% of the first episodes of SE occurring without a known diagnosis of epilepsy[4]. The common causes in adults are low levels of anti-epileptic drugs and cerebrovascular diseases[4-7], followed by infections[8], metabolic disorders, alcohol misuse, and tumors.

A national study[9] on 12,367 patients conducted in Thailand found similar predictors. Still, it included the female gender and the presence of SE complications (e.g., respiratory failure, sepsis) as significant factors for poor outcomes. A prospective study[6] of 18 intensive care units conducted in France determined that the presence of a cerebral insult and the development of refractory SE were significant additional factors associated with poor outcomes. Mortality rates vary among different populations. The literature[10] highlights that, over 16 years, an estimated 80,307 SE patients had an overall mortality rate of 14.9%. The numbers were significantly higher in the elderly, at 24.9%. Conversely, data from the US and UK[11,12] have reported rates of 9.2% and 9.7%, respectively. The earlier literature on this subject indicates that the mortality rate depends on the cause, and literature found that acute symptomatic etiologies such as anoxia, hypoxia, strokes, and central nervous system (CNS) infection (71%, 53%, 33%, and 24% respectively) contribute to increased mortality[4,10,11]. The chronic causes linked to higher death rates include central nervous system (CNS) tumors, idiopathic causes, and alcohol misuse (30%, 25% and 20%, respectively)[4]. Mortality is also found to be higher in patients with refractory SE (RSE), defined as SE unresponsive to treatment with 2 antiepileptic drugs or requiring anesthetic agents for seizure control. Indeed, one study[13] found that in-hospital mortality occurred in 31.75% of RSE patients.

The studies conducted in Saudi Arabia on adult patients with SE are limited. While reviewing the available literature, we observed numerous studies focusing on the outcomes of SE in the pediatric population. Still, only limited clinical studies have concerned the adult population in Saudi Arabia. In light of this gap, the present study aimed to investigate the clinical presentation, causes of complications, and predictors of outcomes in patients with SE who sought treatment at King Saud University Medical City (KSUMC), a prominent referral hospital in Saudi Arabia.

MATERIAL AND METHODS

Study design and settings

This retrospective cohort study was conducted in the Department of Medicine, Neurology Division, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

Data collection

After obtaining ethical approval, data were collected through a retrospective, systematic chart review of all patients admitted to King Saud University Medical City, Riyadh, KSA, a tertiary care university hospital in Riyadh, Saudi Arabia, that provides outpatient, inpatient, cardiac, and intensive care services.

The present study included patients aged 14 years and older who were recruited between May 2015 and December 2023 and met the diagnostic criteria for SE. Patients with missing data or those lost to follow-up were excluded from the study. After applying this criterion, 38 patients were enrolled. The following variables were collected from the patient's medical records: age, gender, history of epilepsy and compliance with medications, seizure type and presence of focal deficit, the duration of SE, presence of refractory SE or new SE onset during admission, presence of autoimmune disease and other comorbidities, onset of complications during admission, or abnormal results in electroencephalogram (EEG), neuroimaging, or cultures. After recording data from medical records, we used the Glasgow Outcome Scale (GOS) as the primary prediction tool for patients' outcomes. GOS is a global tool used to classify patients' functional outcomes. This scale reflects the patients' mortality and morbidity by scoring them from 5 (no or mild disability) to 1 (death). After managing their SE episode, the score is calculated based on their functional status upon discharge (Table I). GOS has two categories based on the score: good outcome (GOS score=5) and poor outcome (GOS score <5).

Ethical considerations

This study was approved by the Institutional Review Board of the College of Medicine at King Saud University, Riyadh, Saudi Arabia (Ref #IRB KSU-21/0724/IRB, dated 23/8/2021).

The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). The study participants provided their written consent upon hospital admission for the use of their medical records solely for research purposes.

Statistical analysis

Data were analyzed using SPSS version 25.0 statistical software (IBM Corp., Armonk, NY, USA), with the level of significance set at a two-tailed, type I error p-value<0.05. We used descriptive statistics, including mean, standard deviation, frequencies, and percentages, to describe both quantitative and categorical variables. Univariate analysis was performed to identify predictors of SE based on GOS scores, with associated p-values, Odds Ratios (OR), and 95% Confidence Intervals (95% CI). To maintain ethical standards, all participants' anonymity was assured by assigning each patient a code number for analysis. Additionally, patient files were not shared or disclosed to anyone outside the researchers' group.

Table I. Glasgow outcome scale.

Category	Classification	Description
1	Death	Death
2	Vegetative state	Unresponsive with absent higher cognitive functions
3	Severe disability	Requires assistance with activities of daily living (ADLs)
4	Moderate disability	Independent with ADLs but requires some assistance
5	Mild or no disability	Complete recovery or minor disability, able to participate fully in daily life

RESULTS

Thirty-eight patients with 'Status Epilepticus' from 14 were included in the analysis. The median age was 30 years (IQR: 22.75, 62.25). Males accounted for 60.5% of cases. Further, 57% of subjects had various medical comorbidities, among which 61.99% had hypertension and 57.14% had diabetes. Autoimmune diseases are present in 18.4% of cases. Out of the 38 patients, 78.9% had a previous history of epilepsy, with 76.39% already on anti-epileptic medications. However, 23.7% of cases showed poor compliance with anti-epileptic medication. The generalized seizure type was seen in 89.5% of cases, and the focal type in 10.59%. Eight per cent had focal neurological signs at presentation, while 23.79% had RSE. The EEG findings revealed that 56.5% of the samples had epileptiform seizure activity, while 43.5% had encephalopathy. Regarding complications, 36.89% of patients experienced respiratory complications, and 23.7% developed acute kidney injury (Table II).

Figure 1 shows the etiology of patients with and without previous epilepsy. Drug reduction or withdrawal was reported in 39.5% of cases. Further, 42.1% had systemic infection, 23.7% had cerebrovascular disease, 10.5% had metabolic disease and head trauma, 7.9% had anoxia, and 2.6% had alcohol withdrawal and autoimmune encephalitis.

In our sample, 56.5% and 43.5% of patients had good and poor outcomes, respectively (Table III). Univariate analysis revealed the following factors as statistically significantly associated with GOS scores: RSE (p=0.043), respiratory complication (p=0.002), acute kidney injury (p=0.043), drug reduction/withdrawal (p=0.024), and cerebrovascular disease (p=0.009). Specifically, the rate of drug reduction or withdrawal was 6 times higher among those with good outcomes. The mortality rate was reported as 18.4%. The Pearson Fisher

Table II. Patients' characteristics.

Demographics	Number (%)/Median (IQR)
Age (year)	30 (22.75, 62.25)
Male	23 (60.5)
Female	15 (39.5)
Presence of medical co-morbidities	22 (57.9)
Presence of autoimmune disease	7 (18.4)
Epilepsy	
Previous history of epilepsy	30 (78.9)
Use of anti-epileptic medications	29 (76.3)
Poor compliance with anti-epileptic medication	9 (23.7)
Status epilepticus	
Seizure type classification	
Generalized	34 (89.5)
Focal	4 (10.5)
New-onset SE in hospital	9 (23.7)
Focal neurological sign at presentation	3 (7.9)
Refractory status epilepticus	9 (23.7)
Duration of status epilepticus	18 (47.4)
Recurrent seizure without regaining consciousness for between 1-100 minutes	20 (52.6)
Investigations at admission	
Normal EEG	4 (14.8)
Abnormal EEG	23 (85.2)
Encephalopathy	10 (43.5)
Epileptic seizure activity	13 (56.5)
Abnormal neuroimaging findings at admission	17 (44.7)
Abnormal electrolytes result at admission	12 (31.6)
Abnormal culture results at admission	11 (28.9)
Complications during admission	
Respiratory complication during admission	14 (36.8)
Acute kidney injury	9 (23.7)
Other complication	6 (15.8)

Status epilepticus (SE), electroencephalogram (EEG).

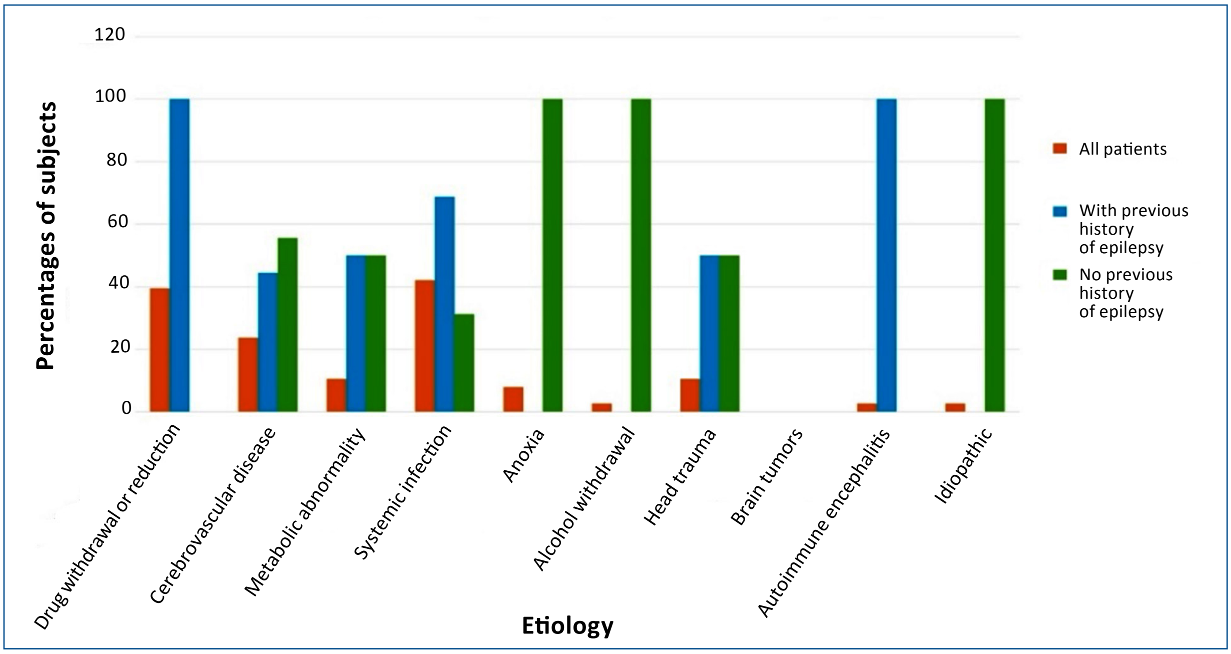


Figure 1. Incidence of etiologies of subjects with status epilepticus (data presented in %).

Exact test revealed statistically significant associations between RSE (p=0.004), respiratory complications (p=0.001), acute kidney injury (p=0.025), and SE due to cerebrovascular disease (p=0.004) with mortality. Among those who died, 100% had respiratory complications, while 71.4% had RSE, acute kidney injury, or cerebrovascular disease.

DISCUSSION

This study analyzed the clinical presentation, causes, and complications while investigating the predictors of SE outcomes in adult Saudi Arabian patients. The present study revealed a high prevalence of SE among young patients in Saudi Arabia, with anti-epileptic medication withdrawal and systemic infections being significant causes. RSE, respiratory complications and status epilepticus resulting from cerebrovascular disease emerged as significant predictors of poor outcomes.

Comparing our study's findings with the literature revealed notable similarities and differences. Gender is often considered a factor influencing differences in the incidence of SE. Although global studies[10] have shown variability in SE incidence between males and females, our study and other regional studies from Egypt and the Aseer region of Saudi Arabia[14,15] observed a higher incidence of SE in males. However, the male predominance may be attributed to gender bias in health services utilization in the region[16].

In contrast to other studies[10,17], most of our patients were young, with a median age of 30 and 73%, ≤59 years old. This may be explained by the fact that the Saudi population is predominantly young. The most prevalent type of SE seizure in our study was generalized, accounting for 89.5%, while focal seizures made up 10.5%. Other studies[6] have shown higher proportions of focal seizures, with rates of 25.8% and 28% in an extensive community-based survey[18] in Saudi Arabia. No cases of nonconvulsive SE were identified in our research work.

While the literature has highlighted the variability of SE etiology across different populations, with low levels of anti-epileptic drugs and cerebrovascular diseases being common causes in adults[4-7], the prevalence of underlying epilepsy was high in our cohort. Specifically, in contrast to the literature, most of our samples (78.9%) had a previous history of epilepsy and were already on anti-epileptic medications[4]. Poor compliance with these medications was observed in 30% of patients.

Consistent with other studies[19], antiepileptic drug reduction or withdrawal was the most common etiology (55.6%) in patients with preexisting epilepsy. In the general population, in keeping with a recent local study[15], systemic infection (42.1%) was identified as the leading cause of SE, followed by drug reduction or withdrawal at 39.5%, cerebrovascular disease at 23.7%, metabolic disease and head trauma at 10.5%, anoxia at 7.9%, autoimmune encephalitis and alcohol withdrawal at 2.6%. None of our patients developed SE in this study due to CNS infection.

Table III. Predictors of status epilepticus outcome based on the Glasgow Outcome Scale (GOS).

Associated factors	No. (%)			Univariate analysis		
	Patients N (%)	Poor outcome (GOS<5)	Good outcome (GOS=5)	*p*-value	Odds ratio	95% confidence interval
Male	23 (100)	10 (43.5)	13 (56.5)	0.298	2.115	(0.516, 8.668)
Female	15 (100)	4 (26.7)	11 (73.3)			
Presence of medical co-morbidities	22 (100)	10 (45.5)	12 (54.5)	0.202	2.5	(0.611, 10.228)
Focal neurological signs at presentation	3 (100)	1 (33.3)	2 (66.7)	0.896	1.182	(0.097, 14.347)
New-onset SE in hospital	9 (100)	5 (55.6)	4 (44.4)	0.191	0.360	(0.078, 1.666)
Duration of SE	20 (100)	9 (45.0)	11 (55.0)	0.275	2.127	(0.548, 8.259)
Recurrent seizure without regaining consciousness for between 1-100 minutes	18 (100)	5 (27.8)	13 (72.2)			
Refractory status epilepticus	9 (100)	6 (66.7)	3 (33.3)	0.043*	0.190	(0.038, 0.950)
Abnormal EEG	23 (100)	9 (39.1)	14 (60.9)	0.99	–	–
Abnormal neuroimaging findings at admission	17 (100)	9 (52.9)	8 (47.1)	0.070	0.278	(0.070, 1.109)
Abnormal electrolytes at admission	12 (100)	5	7	0.676	0.741	(0.182, 3.016)
Abnormal culture at admission	11 (100)	5 (45.5)	6 (54.5)	0.484	0.60	(0.143, 2.511)
Drug reduction or withdrawal due to poor compliance	15 (100)	2 (13.3)	13 (86.7)	0.024*	7.091	(1.297, 38.765)
Cerebrovascular disease	9 (100)	7 (77.8)	2 (22.2)	0.009*	0.091	(0.015, 0.543)
Metabolic disorders	4 (100)	3 (75)	1 (25)	0.130	0.159	(0.015, 1.713)
Systemic infection	16 (100)	8 (50.0)	8 (50.0)	0.157	2.667	(0.687, 10.356)
Anoxia	3 (100)	3 (100)	–	–	–	–
Alcohol withdrawal	1 (100)	–	1 (100)	–	–	–
Head trauma	4 (100)	1 (25)	3 (75)	0.608	1.857	(0.174, 19.8)
Autoimmune encephalitis	1 (100)	–	1 (100)	–	–	–
Cryptogenic/idiopathic	1 (100)	–	1 (100)	–	–	–
Respiratory complication	14 (100)	10 (71.4)	4 (28.6)	0.002*	0.080	(0.016, 0.388)
Acute kidney injury	9 (100)	6 (66.7)	3 (33.3)	0.043*	0.190	(0.038, 0.950)
Other complications	6 (100)	3 (50)	3 (50)	0.471	0.524	(0.090, 3.041)

*Statistically significant.

Previous studies[1,6] have identified factors associated with poor SE outcomes. Therefore, we observed poorer outcomes in patients with new-onset SE in the hospital and refractory SE[1,6]. However, focal neurological signs were rarely observed in our sample. Out of the three patients who did exhibit these signs, most did not have poor outcomes. However, this discrepancy may be due to the small sample size.

Several studies[1,9] have further highlighted that the outcomes of SE are strongly influenced by its underlying cause. Our study findings support these observations, with cerebrovascular disease being significantly associated with poor outcomes, while drug reduction/withdrawal due to poor compliance was associated with better outcomes. This finding underscores the importance of addressing the root cause in managing SE. Additionally, experiencing one or more complications of SE has been linked to poor outcomes[1,9]. In our study, 73.7% of patients experienced one or more complications. Most notably, respiratory complications emerged as significant predictors of mortality in our cohort. Remarkably, all patients who died had respiratory complications, highlighting the critical importance of early recognition and management of medical complications in SE patients. While literature[10-12] have reported mortality rates ranging from 9.2% to 24.9%, our study identified a mortality rate of 18.4%. Among the patients who died, 71.4% had cerebrovascular disease, 28.6% had anoxia, and 14.3% had either a metabolic abnormality, systemic infection, or head trauma. None of the patients with drug reduction or alcohol withdrawal succumbed to mortality. This aligns with findings from other studies[13] that identified cerebrovascular disease as the leading etiology associated with mortality.

Study strengths and limitations

Similar to other studies, this study has certain limitations that should be mentioned. Firstly, the sample size of 38 patients is relatively small, as indicated by the wide confidence intervals observed for certain variables. This could be attributed to the strict inclusion criteria, where patient records were manually reviewed and those with missing data were excluded. However, it is essential to acknowledge a lack of research on the outcome of SE in our region. To our knowledge, only one local study in Saudi Arabia[15] has been conducted on this topic, with just 19 patients included, which reported near-complete recovery without complications in all cases. Our findings align more closely with broader global studies that typically involve larger groups. Future research with larger samples is thus crucial to enhance the understanding and generalizability of our findings. Another limitation is the lack of data regarding the precise duration of SE and the time it took to control seizures. We attempted to collect this information; however, we were regrettably only able to gather this crucial data for a limited number of patients. This suggests that the documentation of seizure timing has received inadequate attention, highlighting a significant need to enhance documentation efforts.

CONCLUSIONS

The present study revealed a high prevalence of SE among young patients in Saudi Arabia, with poor compliance to anti-epileptic medication and systemic infections emerging as primary etiologies. RSE, respiratory complications, acute kidney injury, and SE resulting from cerebrovascular disease all emerged as significant predictors of poor outcomes, emphasizing the importance of addressing the underlying cause of SE and ensuring early recognition and management of complications. Further research into larger samples is needed to validate these findings.

Conflict of Interest
The authors declared no potential conflicts of interest.

Acknowledgements
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Ethics Approval
This study was approved by the Institutional Review Board of the College of Medicine at King Saud University, Riyadh, Saudi Arabia (Ref #IRB KSU-21/0724/IRB, dated 23/8/2021). The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013).

Informed Consent
The study participants provided their written consent upon hospital admission for the use of their medical records solely for research purposes.

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Data Availability
Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

BA: study concept, supervision, manuscript writing and editing: SAA, LA, JA, ZA, and WP: literature review, data collection, analysis and manuscript writing.

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