Archives of Epilepsy

Original Article

Etiology, Clinical Characteristics and In-hospital Mortality of Status Epilepticus: Single Center Experience

Furkan Sarıdaş, Bedirhan Mengüç, Aylin Bican Demir, İbrahim Bora

Bursa Uludağ University Faculty of Medicine, Department of Neurology, Bursa, Turkey

Cite this article as: Sarıdaş F, Mengüç B, Bican Demir A, Bora İ. Etiology, Clinical Characteristics and In-hospital Mortality of Status Epilepticus: Single Center Experience. *Arch Epilepsy.* 2023;29(1):21-25.

Corresponding Author: Furkan Sarıdaş MD, E-mail: furkansaridas@uludag.edu.tr
Received: 07.09.2022 **Accepted:** 03.01.2023 **Publication Date:** 10.03.2023
DOI: 10.4274/ArchEpilepsy.2023.22057

Abstract

Objective: Status epilepticus (SE) is a serious neurological emergency that can has high morbidity and mortality rates and requires prompt diagnosis and treatment. There are different etiologies and the prognosis varies multifactorially. The aim of this study was to reveal the etiological causes, clinical features and mortality rates of patients diagnosed with SE at our center.

Methods: The records of 234 patients with a diagnosis of SE over the age of 18 who were followed up and treated at our center between 01.01.2015-01.01.2022 were evaluated retrospectively. Using the hospital information operating system database, we identified people hospitalized with an International Classification of Diseases 10th Revision code G41 for SE as the primary diagnosis. Demographic information, clinical characteristics, and discharge results were obtained from medical records.

Results: One hundred-twenty (51.3%) female and 114 (48.7%) male patients were evaluated. The top 3 most common etiologic causes were: discontinuation of anti-seizure treatments without advice (n=82), cerebrovascular events (n=50), and meningitis or encephalitis (n=39). Motor seizures were detected in 183 (78.2%) patients, and non-motor seizures were detected in 51 (21.8%) patients. Seizures were suppressed by first-line treatment in 24 patients and by second-line treatments in 135 patients. Seventy-five patients whose seizures could not be suppressed were accepted as refractory SE and 9 died. The mean age of all patients was 55, and 63 of the patients died.

Conclusion: In this study, clinical and demographic features, the etiological causes and in the hospital mortality rates of SE followed in a single center in the Turkish population were determined. The most common causes of patients diagnosed with SE were discontinuation of anti-seizure treatments without our recommendation, cerebrovascular diseases and central nervous system infections, respectively. In our center, no relationship was found between age and mortality. The in-hospital mortality rate was 3.9% for all patients (n=234) and 12% for patients with refractory SE (n=75).

Keywords: Status epilepticus, status epilepticus etiology, status epilepticus in-hospital mortality

INTRODUCTION

Status epilepticus (SE) is defined as a seizure that lasts longer than expected, or the recurrence of many seizures without any improvement in the newly developed condition. The duration of sustained seizure activity used for the above definition varied over time. In 2015, the International League Against Epilepsy (ILAE) specified two different temporal concepts for the definition of SE - t1 (five min; time when ongoing seizure activity is abnormally prolonged, unlikely to stop spontaneously, and when treatment for SE should be initiated) and t2 (30 min; when continued seizure activity poses a significant risk of long-term complications). Accordingly, SE is the condition that results from the failure of the mechanisms responsible for seizure termination or the initiation of mechanisms that lead to abnormally prolonged seizures. Depending on the type and duration of seizures, neuronal damage occurs because of neuronal death and neuronal networks change. Semiologically, it is divided into two groups - convulsive and non-convulsive SE. A continuous seizure lasting 5 min or longer, or 2 or more consecutive seizures in which there is no complete recovery of consciousness between, is currently considered generalized convulsive SE. Refractory SE is a condition that does not respond to first-line and second-line medical treatments and exceeds 30-60 minutes. SE is a relatively common medical and neurological emergency that requires prompt evaluation and treatment. There are different SE syndromes, which differ in etiological factors, prognosis, and treatment, as defined by clinical features and electroencephalography (EEG) findings. Optimal evaluation and treatment can only be performed by understanding the type of SE presented and its underlying cause. Causes, risk factors, and prognosis of SE may vary among centres, regions, and countries. In this study, clinical and demographic features, the etiological causes, treatment and mortality of convulsive SE cases followed up and treated in our hospital in the last 7 years were evaluated.

METHODS

Data Source

In this retrospective survey, the hospital information operating system used inpatient and emergency neurology consultation patient medical records. The information provided mandatory information on diagnosis, demographic data, clinical features, anti-seizure treatments, complications, etiologic causes and discharge information (exitus or discharge) for each patient department. Diagnoses are coded according to International Classification of Diseases 10th Revision (ICD-10). Information about the primary diagnosis and main reasons for referral was mandatory and limited to a single diagnosis, whereas additional diagnoses were optional. The type of epileptic seizures and the diagnosis of SE were made by experienced epileptologists according to the 2015 ILAE classification, by evaluating 21 probe pairs of double banana montage EEG images.[1] Hypoglycemia, uremia due to renal failure, electrolyte imbalances, sepsis and liver failure were evaluated as metabolic disorders. Approval for the study was obtained from the Clinical Research Ethics Committee of Bursa Uludağ University Faculty of Medicine with the decision dated 19.04.2022 and numbered 2022-9/10.

Inclusion Criteria

Individuals with a primary diagnosis of SE were identified according to G41 ICD-10 codes (G41.0, G41.1, G41.2, G41.8, G41.9). Patients over the age of 18 who were first diagnosed or discharged between 01.01.2015-01.01.2022 with the primary diagnosis code G41 in the database were included in the study.

Exclusion Criteria

Patients under 18 years of age were not included for the initial evaluation. Then, 313 medical file records were reviewed. 12 patients were excluded from the evaluation due to insufficient data records, 27 because they were followed up in another institution, and 40 because the etiology could not be determined. The remaining 234 patient records were evaluated.

Statistical Analysis

The analysis of the research data was performed using the Statistical Package for the Social Sciences 28 statistical package program in the computer environment. Frequency, percentage, mean and Mann-Whitney U test were used in the analysis of the data.

MAIN POINTS

- In the etiology, cerebrovascular diseases are the most common cause after treatment-related causes.
- Status epilepticus (SE) is a neurological emergency. In the management of SE, rare causes should be noticed, identified, and treated quickly.
- The primary determinant of prognosis is the etiology of SE. In addition, the accompanying complications during the treatment management and the patient's comorbidities also affect mortality. Therefore, a multidisciplinary approach is required to reduce SE mortality.

RESULTS

One hundred-twenty (51.3%) patients were female and 114 (48.7%) were male, and the mean age was 55 (18-90). Motor seizures (focal, generalized or unknown onset, and seizures that begin focally and progress to bilateral tonic-clonic seizures) were detected in 183 (78%) patients, and non-motor seizures (focal, generalized or unknown onset) were detected in 51 (22%) patients. When the etiology of SE in the cohort was examined, the most common causes were reduction or discontinuation of anti-seizure treatments other than our recommendation 35% (n=82), cerebrovascular events 21% (n=50) and acute central nervous system infections or inflammation 17% (n=39) (Table 1). Patients who did not comply with the anti-seizure drug treatment recommendations had different epileptic syndromes and were using different combination therapies. None of the patients who developed SE were due to mono-therapy discontinuation. All patients developed after the discontinuation of dual-therapy. Because of the fact that the previous follow-ups of the patients occurred in more than one external center, the duration of discontinuation could not be evaluated precisely. Half of the patients who developed SE after a cerebrovascular attack had ischemic cerebrovascular disease in the form of major stroke. Subsequently, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage and intracranial venous sinus thrombosis were seen, respectively (Table 1). The causes of encephalitis were herpes simplex (n=17), other viral encephalitis (n=8) and limbic encephalitis [GAD antibody (n=3), anti-LGI1 antibody (n=1) and VGKC antibody (n=1)]. There were 9 cases of meningitis, including 1 neurosyphilis, 1 HIV-related diagnosis, and 7 cases of acute bacterial meningitis. The causes of hypoxic ischemic encephalopathy were myocardial infarction (n=6), carbon monoxide intoxication (n=4), respiratory arrest due

Table 1. Etiology of status epilepticus

Etiology			n=234
Reduction or discontinuation of anti-seizure treatments without recommendation			82 (35%)
Cerebrovascular events	Major ischemic stroke	24 (48%)	50 (21%)
	Intracerebral hemorrhage	15 (30%)	
	Subarachnoid hemorrhage	5 (10%)	
	Subdural hemorrhage	3 (6%)	
	Intracranial venous sinus thrombosis	3 (6%)	
Acute central nervous system infections or inflammation	Encephalitis	30 (78%)	39 (17%)
	Meningitis	9 (%22)	
Antibiotics			18 (8%)
Intracranial space-occupying lesions			15 (6%)
Hypoxic ischemic encephalopathy			14 (6%)
Metabolic disregulation			11 (5%)
Idiopathic or first seizure			4 (2%)
After SARS-CoV-2 vaccination (Pfizer/BioNTech)			1

SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2

to respiratory tract disease (n=2), and drowning (n=2). Metabolic causes of SE were renal and/or hepatic failure (n=8; 3 renal failure, 3 hepatic failure and 2 patients combined), hyponatremia (n=2) and hypoglycemia (n=1). When the patients who developed SE after the use of antibiotics were evaluated, it was observed that the use of cephalosporin group antibiotics, mostly in the third generation, was observed in all patients. Our patients did not have a history of head trauma, nor had they undergone previous neurosurgery operation. Four cases of SE were evaluated as the first epileptic seizures and subsequently diagnosed as epilepsy.

All patients included in the evaluation (n=234) were treated according to the SE protocol (Table 2). Intravenous benzodiazepine therapy was administered as the first step. Seizures of 24 patients stopped after intermittent diazepam treatment. Subsequently, as a second-line treatment; 183 treatment doses of levetiracetam the, 86 phenytoin and 10 valproic acid were administered intravenously to 210 patients whose seizures continued. Topiramate was administered in 8 patients and lacosamide in 16 patients via the enteral route (with feeding tube). As third-line treatment in 75 resistant cases; 75 treatment doses of midazolam, 18 thiopental and 7 doses of ketamine were administered (Figure 1). Refractory seizures requiring anesthetic treatment developed in 32% (n=75) of the patients. All these patients were followed up with invasive mechanical ventilation. Nine cases (5 female and 4 male, mortality 3.9% for the whole series, 12% for refractory series) died. The average hospital stay was 26 (9-88) days. The mean age of the patients with exitus was 63 (41-87).

Midazolam was the first choice in all patients in terms of anesthetic agents applied to patients with resistant seizures. Additionally, ketamine (n=3) or thiopental sodium (n=1) treatment was administered to all patients who died. Some etiological factors and many accompanying comorbidities were detected in the patients (Table 3). No significant difference was found when the mean age of all SEs and the patients who died were compared (55;63, p>0.05).

DISCUSSION

SE is a life-threatening medical emergency that requires immediate medical treatment and is associated with morbidity and mortality. In published studies, the incidence of SE varies between 10 and 20 or 40 per 100,000.[2] Different results between male and female genders were reported in some studies.[3,4] Causes of SE such as cerebrovascular diseases, anoxia, neurodegenerative diseases and brain tumors increase significantly after the age of 60. Between 6 and 20% of SE patients are diagnosed the first time they experience a seizure in their life.[5] In our series, only 4 (2%) patients were idiopathic or had a first seizure when the group whose cause could not be clarified was excluded. The reason for this low rate may be that our institution is a tertiary hospital and it is a hospital where complicated patients are followed or referred rather than newly diagnosed patients.

The most common causes of SE are inappropriate use of anti-seizure therapy and ischemic stroke.[5] Acute symptomatic causes are more common than chronic symptomatic causes, and of these, a stroke is the most common.[3] A history of at least one epileptic episode was

Table 2. Status epilepticus treatment protocol applied to patients

First line	Second line	The third line	Enteral treatment
Diazepam: IV 10 mg, <5 mg/min bolus, repeated within 5 min at 10 mg doses	Levetiracetam: IV, 30-40 mg/kg up to a maximum of 4000 mg, infusion in 10 min	Midazolam: IV, 0.2 mg/kg bolus, followed by 1-4 mg/kg/hr infusion	Topiramate: 200 mg twice daily followed by a 500-1000 mg loading dose
	Phenytoin: IV, 15-20 mg/kg, 50 mg/min infusion, half the infusion rate in elderly patients	Thiopental: IV, 3-5 mg/kg loading and 1-6 mg/kg/hr infusion/10 mg/kg bolus and 1-3 mg/kg/hr infusion	Lacosamide: 100-200 mg twice a day following a 200-400 mg loading dose
	Valproic acid: IV, 15-20 mg/kg, 5 mg/kg/min infusion	Ketamine: IV, 2 mg/kg bolus followed by 2-4 mg/kg/hr infusion	

IV: Intravenous

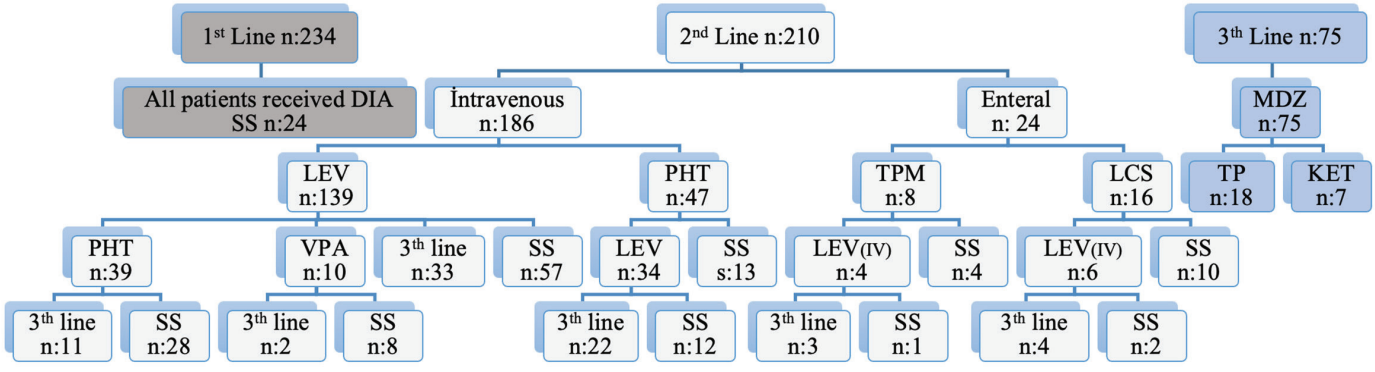

Figure 1. Treatment features
DIA: Diazepam, LEV: Levetiracetam, PHT: Phenytoin, VPA: Valproic acid, TPM: Topiramate, LCS: Lacosamide, MDZ: Midazolam, TP: Thiopental, KET: Ketamine, SS: Seizure suppressed

Table 3. Clinical features of exitus cases due to status epilepticus

Age	Sex F/M	Etiology	Anesthetic treatment	Comorbidity
41	F	Resistant epilepsy	Midazolam	-
68	M	Intracranial mass, limbic encephalitis (LGI)	Midazolam + ketamine	Aspiration pneumonia
65	M	Meningitis, acute kidney failure	Midazolam	Mesothelioma-associated pneumosepsis
81	M	3rd Generation Cephalosporins (ceftriaxone and cefepime) and intracerebral hemorrhage	Midazolam + ketamine	Hypertension, chronic renal failure, rheumatoid arthritis, urosepsis
66	M	Meningitis and hyponatremia	Midazolam + ketamine	Pituitary adenoma
45	M	Cardiac arrest; hypoxic ischemia	Midazolam	Ankylosing spondylitis, chronic kidney failure
87	F	Diabetic ketoacidosis	Midazolam + thiopental sodium	Diabetes mellitus, chronic obstructive pulmonary disease, dementia
41	M	Brain metastasis (of breast cancer)	Midazolam	Sepsis, breast cancer, disseminated intravascular coagulation
73	F	3rd Generation Cephalosporin (ceftriaxone)	Midazolam	Breast cancer, ischemic stroke, epilepsy, covid pneumosepsis, chronic obstructive pulmonary disease

F: Female, M: Male

reported before admission in 35% of patients diagnosed with SE. In general population studies, 12-50% of patients diagnosed with SE are patients with a previous diagnosis of epilepsy.[6] Consistent with the literature in our study, 82 patients (35%) were diagnosed with epilepsy or had at least one epileptic episode before. Etiologies may differ between societies. Central nervous system infections are more common in developing countries.[4] However, the variability of the regional or patient groups included in the studies creates etiological differences in the studies. In our study, the most common (35%) etiology of SE was discontinuation of anti-seizure treatment without our recommendation or use it at inappropriate doses, followed by cerebrovascular diseases (21%) and central nervous system infection/inflammation (17%). Apart from the risk of developing SE and intraparenchymal hemorrhages, no different distribution was found in the literature on cerebrovascular diseases, whereas intracerebral parenchymal hemorrhages were higher than expected in this study as an etiologic cause.[7,8] While the main clinical picture was encephalitis for most of the cases, we found fewer cases of meningitis or meningoencephalitis. We also identified rare causes such as post-vaccination or antibody-associated limbic encephalitis.[9-11] Our case series is largely compatible with the literature for etiological causes. However, we would like to emphasize that the existence of rare factors should not be overlooked and that the etiological evaluation should be conducted in depth.

The etiology of SE is the main determinant of prognosis.[4] As well as the etiology of SE, the problems encountered because of the previous clinical condition of the patient, diagnosis, follow-up and treatment processes have combined and complex effects on mortality. Additionally, SE may not always be easily identified in emergencies, or the underlying cause may not be known. Therefore, the distinction of the cause of mortality cannot be clearly made, and it has been stated in many studies that in some cases it was not possible to establish the real cause of death. The highest mortality risk is seen in acute central pathologies. Mortality due to inappropriate anti-seizure drug intake, toxicity, or metabolic pathologies is relatively low. Additionally, the diagnosis of epilepsy as SE is significantly associated with mortality.[12] Although it was emphasized in some studies that the development of refractory SE is an independent risk factor for mortality in patients followed in the intensive care unit, this relationship is not unclear because it was not possible to evaluate this independently of the cumulative risk of complications.[2,13] While inappropriate anti-seizure therapy has a better prognosis than other etiologies, acute symptomatic SE after a stroke is associated with a higher risk of mortality and morbidity than other SE etiologies. Encephalitis is strongly associated with refractory SE and the risk of developing epilepsy in the follow-up period is quite high. Cryptogenic SE of unknown etiology has been associated with low mortality but a high risk of epilepsy. The patient's age is the third independent risk factor that determines the prognosis, after duration and etiology. Mortality in adult patients ranges increases with age.[5] Prolonged mechanical ventilation with advanced age, coma at admission, hypoxic-ischemic brain injury, accompanying comorbidities, acute symptomatic etiology, and refractory SE are generally associated with higher mortality. However, different results have been reported in many studies in the literature. In this study, the mean age of those who died was found to be older than those in all SEs, but no statistical difference was observed. Additionally, acute symptomatic causes were much more common in this group. However, because of the small number of cases, they were not compared statistically.

When all SE patients were evaluated, mortality varied between 1.9 and 40% in the literature.[2] This rate was 5.6-14% in nonrefractory SE patients, and 17-50% in refractory SE.[6] In our study seven year follow up, 9 patients with a diagnosis of SE died during the hospitalization period. The mortality rate was 3.8% in all patients and 12% in the refractory group. When all cases are evaluated, we think that this rate is good and probably due to the careful evaluation of the diagnosis and treatment processes for the etiology in addition to effective seizure treatment. On the other hand, SE mortality is not only dependent on etiology but is multifactorial due to comorbidities and complications (Table 3). This suggests that serious comorbid diseases, treatments, follow-up in the intensive care unit and complications impact mortality. Considering all these, in the management of SE patients, optimal application of rapid multidisciplinary approaches with teamwork for emergency services, anesthesia and intensive care units and other systemic complications that may accompany may reduce mortality rates. An evaluation of a larger case series with our study methods would further contribute to the literature.

Study Limitations

We planned our study by including individuals with SE using the ICD-10 diagnostic code and presented it as a cohort of 313 cases identified over 7 years. However, 234 patients were evaluated due to insufficient data recording, continued follow-up in another institution, and the etiology could not be concluded with a clear consensus. Additionally, the current search scheme only allows the evaluation of individuals with a definitive diagnosis of SE. All these conditions may be debilitating factors affecting the optimal assessment of the entire SE group.

CONCLUSION

In our single-center observational study of the development of status epilepticus in Turkish society:

1. The 3 most common etiologies in etiology were found to be inappropriate use/stopping of anti-seizure therapy, cerebrovascular diseases, and central nervous system infection/inflammation, respectively. Contrary to expectations, intraparenchymal hemorrhages were more common in etiology. About one in three patients developed refractory SE.

2. In addition to common causes in etiology, rare causes such as anti-GAD, LGI-1, and anti-VGKC, neurosyphilis, HIV-induced central nervous system infections, or Severe acute respiratory syndrome-Coronavirus-2 vaccine (Pfizer/BioNTech) were detected. Rare causes should be considered and evaluated in detail.

3. This study highlights the need to consider the effects of etiologic factors on SE mortality, as well as comorbid conditions and complications. Therefore, in addition to SE treatment, other medical conditions that may develop during this period should be carefully evaluated and treated to reduce mortality rates.

Ethics

Ethics Committee Approval: Bursa Uludağ University Ethics Committee decision no. 2022-9/10 dated 19.04.2022.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.S., A.B.D., İ.B., Concept: F.S., A.B.D., Design: F.S., B.M., Data Collection or Processing: F.S., B.M., Analysis or Interpretation: F.S., A.B.D., Literature Search: F.S., A.B.D., İ.B., Writing: F.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56(10):1515-1523. [CrossRef]
2. Tuppurainen KM, Ritvanen JG, Mustonen H, Kämppi LS. Predictors of mortality at one year after generalized convulsive status epilepticus. *Epilepsy Behav*. 2019;101(Pt B):106411. [CrossRef]
3. Ascoli M, Ferlazzo E, Gasparini S, et al. Epidemiology and Outcomes of Status Epilepticus. *Int J Gen Med*. 2021;14:2965-2973. [CrossRef]
4. Lv RJ, Wang Q, Cui T, Zhu F, Shao XQ. Status epilepticus-related etiology, incidence and mortality: A meta-analysis. *Epilepsy Res*. 2017;136:12-17. [CrossRef]
5. Moghaddasi M, Joodat R, Ataei E. Evaluation of Short-term Mortality of Status Epilepticus and Its Risk Factors. *J Epilepsy Res.* 2015;5(1):13-16. [CrossRef]
6. Langenbruch L, Strippel C, Görlich D, et al. Occurrence of status epilepticus in persons with epilepsy is determined by sex, epilepsy classification, and etiology: a single center cohort study. *J Neurol.* 2021;268(12):4816-4823. [CrossRef]
7. Dinc Y, Biçan Demir A, Bakar M, Bora İ. Evaluation of the relationship between epileptic seizures and type of parenchymal lesion in patients with cerebral venous thrombosis. *J Neurological Sciences and Neurophysiology*. 2022;39:28-34. [CrossRef]
8. Biçan Demir A, Atasayar G, Karli N, Taskapilioglu, O, Kahveci, F. A Case Report of Etiology of Cerebral Venous Sinus Thrombosis Developed After Spinal Anesthesia in Asteroid, Doping Using Young Athlete. *J Neurol Res.* 2014;4(1):37-40. [CrossRef]
9. Kılıç R, Kılıç E, Dinç Y, Demir AB. New onset refractory status epilepticus after BNT162b2 nCoV-19. *J Clin Images Med Case Rep*. 2022;3(5):1855. [CrossRef]
10. Uslusoy H İ, Dinc Y, Bican Demir A, Evaluation of LGI1-antibody Encephalitis, a Rare Cause of Limbic Encephalitis, from Diagnosis to Treatment. *Turk J Neurol*. 2022;28(2):127-128. [CrossRef]
11. Bican Demir A, Uzun P, Taşkapılıoğlu Ö, Bora İ, Tüzün E. Voltaj Bağımlı Potasyum Kanal Antikorlu Bir Limbik Ensefalit Olgusu. *Journal of the Turkish Epilepsy Society.* 2016;22(1):72-75. [CrossRef]
12. Hocker S. Why do patients die after status epilepticus? *Epilepsy Behav*. 2019;101(Pt B):106567. [CrossRef]
13. Hawkes MA, English SW, Mandrekar JN, Rabinstein AA, Hocker S. Causes of Death in Status Epilepticus. *Crit Care Med*. 2019;47(9):1226-1231. [CrossRef]