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# Predictors of outcomes and refractoriness in status epilepticus: A prospective study

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ABSTRACT

*Objective:* The objective of this study was to determine the predictors of outcomes and refractoriness in status epilepticus (SE).
*Methods:* This is a prospective study of 59 adult patients with SE who were admitted to the Emergency Department between February 2012 and December 2013. The effects of clinical, demographic, and electrophysiologic features of patients with SE were evaluated. To evaluate outcome in SE, STESS, mSTESS, and EMSE scales were used.
*Results:* Logistic regression analysis showed that being aged ≥65 years ($p = 0.02$, OR: 17.68, 95% CI: [1.6–198.4]) for the short term and having potentially fatal etiology ($p = 0.027$, OR: 11.7, 95% CI: [1.3–103]) for the long term were the only independent predictors of poor outcomes; whereas, the presence of periodic epileptiform discharges (PEDs) in EEG was the only independent predictor of refractoriness ($p = 0.032$, OR: 13.7, 95% CI: [1.3–148.5]). The patients with ≥3 Status Epilepticus Severity Score (STESS) did not have poorer outcomes in the short- ($p = 0.157$) and long term ($p = 0.065$). There was no difference between patients with 0–2, 3–4, and ≥4 mSTESS in the short- and long term in terms of outcome ($p = 0.28$ and 0.063, respectively). Also, there was no difference between subgroups (convulsive SE [CSE], nonconvulsive SE [NCSE], and epilepsia partialis continua [EPC]) in terms of STESS and mSTESS. When patients with EPC were excluded, both STESS and mSTESS scores of the patients correlated with poorer long-term outcomes ($p = 0.025$ and 0.017, respectively). The patients with ≥64 points in the Epidemiology-based Mortality in SE-Etiology, age, comorbidity, EEG (EMSE-EACE) score and those with ≥27 points in EMSE-Etiology, age, comorbidity (EMSE-EAC) score did not have poorer outcomes in the short term ($p = 0.06$ and 0.274, respectively) while they had significantly poorer outcome in the long term ($p < 0.001$ and 0.002, respectively). In subgroup analysis, patients with CSE with ≥64 points in EMSE-EACE had significantly poorer outcome in the both short- and long term ($p = 0.014$ and 0.012, respectively), and patients with CSE with ≥27 points in EMSE-EAC had significantly poorer outcome in the long term ($p = 0.03$) but not in the short term ($p = 0.186$). Outcomes did not correlate with EMSE scores in patients with NCSE and EPC. Status epilepticus was terminated with intravenous (IV) levetiracetam (LEV) in 68.75% of patients and with IV phenytoin (PHT) in 83.3% of patients. No statistically significant difference was found between the two groups in terms of efficacy ($p = 0.334$).
*Conclusion:* Being aged ≥65 years predicts poor short-term outcomes, and having potentially fatal etiology predicts poor long-term outcomes, which highlight the importance of SE treatment management in the elderly. Both STESS and mSTESS are not predictive for poor outcomes in EPC. Excluding patients with EPC, STESS, and mSTESS could predict poor long-term outcomes but not in the short term in SE. Epidemiology-based Mortality in Status Epilepticus score could predict poor outcome in the long term better than STESS and mSTESS. Specifically, EMSE scores correlated with poor outcome in patients with CSE but not with NCSE and EPC. New scales are needed to predict outcome especially in patients with NCSE and EPC. The presence of PEDs in EEG is a predictor of RSE, and EMSE score can also be used to predict RSE. There was no difference in the efficacy of IV LEV and IV PHT in SE. This study is significant for having one of the longest follow-up periods in the literature.



## 1. Introduction

Status epilepticus (SE) is a major medical and neurologic emergency that has to be treated immediately to avoid severe morbidity and mortality. The outcome of SE is closely related with its etiology. The mortality rate is below 10% in SE, which is mostly caused by alcohol use and discontinuation of antiepileptic drugs (AEDs); the other etiologic factors

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include 26.3% stroke, 31% metabolic disturbances, and up to 60% hypoxia/anoxia-related SE [1]. The outcome of SE is primarily affected by etiologic factors followed by duration of SE, treatment delay, state of consciousness at admission, age, as well as the presence of periodic epileptiform discharges (PEDs) [2].

Refractory SE (RSE) is defined as SE refractory to treatment with first-line benzodiazepines (BZD) and any of the second-line AEDs including phenytoin (PHT), valproic acid (VPA), levetiracetam (LEV), and phenobarbital (PB) or SE that lasts more than 60 min [3,4]. Of all SE episodes, 24–43% is RSE [5–9]. The reported mortality rate of RSE in retrospective studies was 16–23% [3,5,8]. In a prospective study, the mortality rate of RSE was reported as 39%, whereas it was 11% in patients with nonrefractory SE ($p = 0.001$) [6]. Severity of impairment of consciousness, de novo episode, and some patterns of EEG have been shown as independent risk factors for the development of RSE in studies [6,10].

It is important to treat patients with SE, who will have poor outcome, aggressively. However, aggressive treatment may increase morbidity in patients with SE who will have good outcome and who actually do not need aggressive treatment. Thus, scales such as Status Epilepticus Severity Score (STESS), modified STESS (mSTESS), and Epidemiology-based Mortality in Status Epilepticus (EMSE) scores were developed to predict good and poor outcomes and treat patients appropriately.

Our aim was to investigate the relationship between clinical, demographic, and electrophysiologic features and both outcomes and refractoriness in SE in our prospective cohort, which was diagnosed according to the new International League Against Epilepsy (ILAE) SE classification [11]. Also, STESS, mSTESS, and EMSE scores of the patients were evaluated to predict poor outcome.

## 2. Material and methods

### 2.1. Patient selection

This was a prospective cohort of 59 adult patients who were diagnosed as having SE between February 2012 and December 2013 at the Neurology Department of Istanbul Faculty of Medicine. Thirty-one (52.5%) patients were males, and 28 (47.5%) were females. Their ages ranged between 17 and 90 years (mean: $50.9 \pm 18.3$ years). Clinic, demographic, and electrophysiologic features of the patients; their short- and long-term outcomes; and refractoriness of SE were recorded.

The study was approved by the Institutional Ethics Committee of Istanbul University Istanbul Faculty of Medicine (12/1229). Informed consents were obtained from all patients or their legal guardians and controls following provision of detailed information on the study examinations and tests.

### 2.2. Subtypes of status epilepticus

Convulsive status epilepticus (CSE) is defined as one or two seizures without attainment of consciousness in-between, which last longer than 5 min [12]. The diagnosis of EPC is established by the observation of seizure with contractions involving only focal parts of the body and lasting at least 30 min; consciousness is often preserved although various degrees of altered consciousness might be observed [13]. Epilepsia partialis continua of Kojevnikov was divided into three conditions in the ILAE's 2006 classification: as occurs with Rasmussen syndrome, as occurs with local lesions, and as a component of inborn errors of metabolism [14].

A recently published study by Trinka et al. proposed 2-time points for SE. The first-time point (t1) is the time beyond which seizures should be regarded as "continuous seizure activity". The second-time point (t2) is the time of ongoing seizure activity after which there is a risk of long-term consequences including neuronal injury. In the case of convulsive SE, t1 at 5 min and t2 at 30 min were proposed; t1 at 10 min and t2 at >60 min were suggested in cases of focal SE with impaired consciousness; and t1 at 10–15 min and t2 at "unknown time" were suggested in cases of absence status epilepticus. For classification of SE, 4 axes (semiology, etiology, EEG correlates, and age) were proposed. The "semiology" axis refers to the clinical presentation of SE, and clinically, SE is divided into two forms: with or without prominent motor symptoms. "Convulsive" and "nonconvulsive" terms were kept, and EPC was listed under "Focal motor", which was a subgroup of "SE with prominent motor symptoms". Also, no diagnostic criteria were proposed for EPC [11].

The diagnosis of nonconvulsive SE (NCSE) is established through EEG [15].

In our study, one seizure or two seizures without attainment of consciousness in-between, lasting longer than 5 min was accepted as CSE. A seizure with contractions involving only focal parts of the body and lasting at least 30 min, frequently with preserved consciousness, was accepted as EPC. The diagnosis of NCSE was established through an EEG in clinically suspected patients. Generalized myoclonic jerks with or without impairment of consciousness and lasting at least 30 min were accepted as MSE.

### 2.3. Etiology

We classified etiologies as in ILAE's classification: acute, remote, and progressive symptomatic and unknown. We did not have patients with SE in defined electroclinical syndromes [11]. Etiologies that are fatal unless no treatment is given, including acute large vessel occlusion, acute cerebral hemorrhage, acute central nervous system (CNS) infection, severe systemic infection, malignant brain tumor, eclampsia, and AIDS with CNS involvement are defined as "potentially fatal etiologies" [6]. We divided the etiologies of the patients into two groups: 1) patients with potentially fatal etiologies and 2) patients with potentially nonfatal etiologies.

### 2.4. Electroencephalography

Twenty-one channel EEG recordings with electrodes placed according to the International 10–20 System were obtained in the laboratory or at the bedside. Postictal (at 0–2 days after cessation of SE), interictal (at first month after the cessation of SE), and/or ictal EEGs were recorded. Periodic epileptiform discharges and burst-suppression patterns were also investigated, and if found, they were called "poor prognostic findings in EEG".

We used the following criteria [15] for the diagnosis of NCSE in our study: NCSE is the alteration of consciousness or behavior from baseline state for at least 30 min without convulsive movements and involves one or more of the following epileptiform patterns: 1) repetitive focal or generalized epileptiform activity or rhythmic theta or delta activity more than two per second, 2) if these EEG patterns are fewer than one per second, then improvement or resolution of epileptic activity and improvement in the clinical state following intravenous AED, and 3) A temporal evolution of epileptiform or rhythmic activity more than one per second with change in location or frequency over time. The diagnosis of NCSE was established through an EEG in clinically suspected patients. We could not use the Salzburg Consensus Criteria for the diagnosis of NCSE because it was written in 2015, but we collected data from patients with NCSE between 2012 and 2013.

We included patients complying with the following descriptions for periodic discharges and burst-suppression pattern: periodic discharges are stereotyped epileptiform discharges (spikes, polyspikes, sharp waves, sharply contoured slow-waves, or a mixture of spikes and slow-waves) which may be monophasic, biphasic, or triphasic and are usually of high amplitude (100 to 300 μV) which occur at regular or almost regular intervals of 0.3 to several seconds. Periodic lateralized epileptiform discharges (PLEDs) are unilateral. Bilateral PLEDs (BiPLEDs) are the lateralized periodic or pseudoperiodic discharges, which are seen independently over both hemispheres. Generalized periodic