

## The Predictive Factors for Prolonged Seizures and Status Epilepticus: A Single Center Study

### Uzamış Nöbet ve Status Epileptikus için Risk Faktörleri: Tek Merkez Deneyimi

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#### ABSTRACT

**Objective:** To analyze the clinical features of prolonged seizures and status epilepticus and perform risk analysis on super refractory status epilepticus (SRSE) in pediatric intensive care unit (PICU) admissions.

**Method:** Demographic features, underlying etiologies, treatment modalities, electroencephalographic and neuroimaging outcomes of intensive care unit admissions between 2015 and 2019 were analyzed.

**Results:** Seventy-one children were enrolled. The most common etiologic factors for prolonged seizure were fever in 45.1%, (central nervous system infection: 16.9%, infection other than central nervous system: 28.2%), withdrawal of the antiepileptic medication in 40.9%, intoxications in 12.7% of the children and intracranial hemorrhage due to arteriovenous malformation in one (1.4%) patient. At admission hypoglycemia was detected in 23.9%, hypocalcemia in 18.3%, hyponatremia in 15.5%, acidosis in 35.2%, and increased lactate levels in 25.4% of the patients. The patients were grouped based on fever at admission and new-onset seizure. Approximately 45.1% of the population had fever at admission and consisted of younger children compared to their counterparts ( $p=0.023$ ). Children with pre-existing epilepsy had frequent history of sibling death, while patients presented with new-onset seizure had more often significant lactate elevations, acidosis, and required mechanical ventilation at admission ( $p=0.002$ ,  $p=0.008$ ,  $p=0.017$ ). Twelve (16.9%) patients developed SRSE. Low serum sodium and calcium levels increased the risk of developing SRSE (OR: 10.800, 95%CI: 2.518-46.318; OR: 4.554, 95%CI: 1.159-17.892). However PRISM-3 score has been identified as the single independent risk factor for SRSE (OR: 1.174, 95% CI: 1.039-1.327). Three (4.2%) children died of secondary complications during their stay in intensive care unit. Tracheostomy cannulation was performed in two (16.7%) SRSE patients due to neurological incapability to maintain a patent airway.

**Conclusion:** PRISM-3 score is the independent risk factor of SRSE. Electrolyte abnormalities (hyponatremia and hypocalcemia) are associated with developing SRSE.

**Keywords:** Seizure, Status epilepticus, Super refractory status epilepticus, Hyponatremia

#### Öz

**Amaç:** Çocuk yoğun bakım ünitelerindeki uzamış nöbet ve status epileptikusun klinik özelliklerinin analiz edilmesi ve süper dirençli status epileptikusun (SRSE) risk analizinin yapılması

**Gereç-Yöntem:** 2015-2019 yılları arasında çocuk yoğun bakım ünitesine başvuran uzamış nöbet ve status epileptikus olgularının demografik özellikleri, altta yatan etiyolojileri, tedavi modaliteleri, elektroensefalografik ve nörogörüntüleme sonuçları incelendi.

**Bulgular:** Yetmiş bir olgu çalışmaya dahil edildi. En sık etyolojik nedenlerin %45.1'inde ateş (santral sinir sistemi enfeksiyonları: %16.9, santral sinir sistemi dışında enfeksiyonlar: %28.2), %40.9'unda antiepileptik tedavinin kesilmesi, %12.7'nde intoksikasyonlar ve bir olguda (%1.4) arteriovenöz malformasyona bağlı intrakraniyal kanama olduğu gözlemlendi. Başvuru anında %23.9'unda hipoglisemi, %18.3'ünde hipokalsemi, %15.5'inde hiponatremi, %35.2'nde asidoz ve %25.4'ünde artmış laktat seviyeleri saptandı. Olgular, nöbet esnasında ateş varlığı ile önceden geçirilmiş nöbet öyküsü olup olmamasına göre gruplara ayrıldı. Başvuru anında ateş, %45.1'inde mevcut iken, bu olguların afebril nöbet geçirenlere göre daha küçük yaşta hastalardan oluştuğu görüldü ( $p=0.023$ ). Önceden geçirilmiş nöbet öyküsüne sahip olgularda sık kardeş ölüm öyküsünün olduğu, ilk kez nöbet ile başvuran olgularda ise yatış anında laktat yüksekliği ve asidozun belirgin, mekanik ventilasyon gereksiniminin ise sık olduğu gözlemlendi ( $p=0.002$ ,  $p=0.008$ ,  $p=0.017$ ). Oniki (%16.9) hastada SRSE gelişti. Bu olgularda düşük serum sodyum ve kalsiyum seviyelerinin SRSE gelişim riskini artırdığı anlaşıldı (OR: 10.800, 95% CI: 2.518-46.318; OR: 4.554, 95% CI: 1.159-17.892). Çoklu regresyon analizinde, PRISM-3 skorunun SRSE için tek bağımsız risk faktörü olduğu saptandı (OR: 1.174, 95% CI: 1.039-1.327). Üç (%4.2) olgu, çocuk yoğun bakım yatışı esnasında ikincil komplikasyonlar sonucu kaybedildi. SRSE gelişen iki olguda (%16.7) nörolojik olarak hava yolu açıklığını koruyamama nedeniyle trakeostomi kanülizasyonu uygulandı.

**Sonuç:** PRISM-3 skoru SRSE için bağımsız risk faktörüdür. Elektrolit dengesizliği (hiponatremi, hipokalsemi) SRSE gelişimiyle ilişkilidir.

**Anahtar kelimeler:** Nöbet, Status epileptikus, süper dirençli status epileptikus, hiponatremi

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## INTRODUCTION

Seizure is the sudden onset of abnormal electrical discharge owing to excessive or synchronous neuronal activity in the brain <sup>(1)</sup>. In patients with prolonged symptoms, seizures can become a much more complicated, life-threatening condition known as status epilepticus (SE) <sup>(1,2)</sup>. The International League Against Epilepsy (ILAE) has proposed a consensus definition of prolonged seizures and SE. The first dimension of this definition is the time point ( $t_1$ ) at which the seizure should be considered a prolonged seizure, and the second dimension ( $t_2$ ) is the duration of ongoing seizure activity that conveys the risk of long-term consequences. In tonic-clonic seizures, the ILAE task force's novel description of prolonged seizure is epileptic activity of >5 min duration, and of focal seizures, an epileptic activity persisting for >10 min (1). The danger of prolonged seizure is seizure-related irreversible neuronal damage <sup>(3,4)</sup>.

Several studies have addressed important aspects of SE in terms of its etiology and incidence. Both the incidence of SE and SE-related mortality vary greatly, ranging from 5.2 to 12.4 per 100,000 <sup>(5)</sup>. In a 2017 meta-analysis, new onset of symptomatic etiology was reported to be the leading cause of etiology-specific SE (odds ratio [OR]: 0.411; 95% confidence interval [CI]: 0.315–0.507) <sup>(6)</sup>. SE may be the condition underlying several neurologic disorders, including epileptic syndromes, rather than a syndrome or disease in itself <sup>(7)</sup>. The most prevalent cause of SE in children is febrile seizure, but fever may also be the triggering factor in patients with previously diagnosed epilepsy <sup>(8)</sup>. The other causes of SE are abnormalities as seen on neuroimaging, inborn errors of metabolism, electrolyte imbalances, intoxication, central nervous system (CNS) infections, and autoimmune disorders <sup>(9)</sup>.

Immediate therapy plays a crucial role in seizure termination, as mortality may otherwise reach 22% <sup>(7,10)</sup>. Almost 80% of seizures are successfully managed by first-line anti-seizure drugs <sup>(11)</sup>, but in the remaining 20%, seizure activity may fail to cease in response to first- or second-line therapies (benzodiazepine and anticonvulsive drugs) and will progress to refractory SE (RSE).

Super RSE (SRSE) is defined as the persistence of seizure activity for >24 h and requires the administration of general anesthesia drugs <sup>(12,13)</sup>. The annual incidence of SE is 12–23 episodes per 100,000 children, with 10–40% developing RSE <sup>(14,15)</sup>. The incidence of SRSE reported in 602 convulsive children was 7.14% <sup>(16)</sup>. However, neurological complications are not the only concern in the management of convulsive children. Even if many SRSE episodes are successfully managed with aggressive anti-seizure therapy, the typically prolonged pediatric intensive care unit (PICU) stay may lead to secondary complications of infections, drug-related adverse effects, or hematologic complications <sup>(17)</sup>. Consequently, predicting the risk of SRSE is of paramount importance in PICU management. The current study analyzed PICU admissions in children with prolonged seizures, including a risk analysis for subsequent SRSE. The demographic and clinical features, underlying etiologies, treatment modalities, electroencephalography (EEG) and neuroimaging findings, and metabolic states of the children prior to PICU admission were therefore evaluated.

## PATIENTS AND METHODS

The study protocol was approved by the local ethics committee and followed the principles for human investigations outlined in the Second Declaration of Helsinki (date, April 17, 2019; no.: 2019-04/02). Parental consent for study participation was not required due to its retrospective design.

The study was conducted at the Sivas Cumhuriyet University Faculty of Medicine. The hospital includes a level-III, high-volume-referral intensive care unit with 8-bed capacity (600-750 admissions / per year) for the densely populated territory around the central Anatolia region. All intensive care admissions manifesting prolonged seizure (seizure lasting more than five minutes that occur either at the emergency room, pediatric ward or during PICU stay) between January 2014 and January 2019 were enrolled in the study. Demographic and other data, including those on underlying chronic conditions, history of epilepsy, and anti-seizure medications, were extracted from the electronic database. Data on seizure etiology, duration of seizure prior to PICU admission, metabolic state at initial PICU admission, and clinical

features, including endotracheal intubation, PRISM-3 score, treatment modalities, EEG monitoring, and CNS neuroimaging were collected. Etiologic factors for seizures were classified as: i) withdrawal of the antiepileptic drug, ii) fever (meningitis/encephalitis or infections other than those of the CNS), iii) intoxications, and iv) structural abnormalities of the CNS.

The group categorizations were based on the presence of fever (seizures with and without fever) and a new-onset seizure (children with a history of epilepsy vs. those with a new-onset seizure). Children progressing to SRSE were identified, and their data analyzed accordingly.

Abnormal biochemical features were identified in laboratory tests of venous blood samples or blood gas analysis at initial PICU admission, including hyponatremia (serum sodium <135 meq/L) <sup>(18)</sup>, hypoglycemia (serum blood glucose <60 mg/dL), hypocalcemia (serum calcium <8.5 mg/dL and blood gas ionized calcium <1 mmol/L), elevated lactate (blood gas lactate >2 mmol/L), and metabolic acidosis (blood gas pH <7.35, HCO<sub>3</sub> <15 meq/L, BE > -5).

In the absence of continuous EEG monitoring in the PICU, EEG monitoring was conducted twice a day (30–45 min/session). The recording data were analyzed according to epileptic activity (generalized vs. focal), background activity (normal vs. abnormal), and the acquired burst-suppression pattern. Neuroimaging, either computed tomography (CT) or magnetic resonance imaging (MRI) was conducted before discharge.

### Statistical analysis

SPSS version 22 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. Descriptive variables were expressed as percentages (%), the means ± standard deviation, or medians with interquartile ranges (IQRs) in parentheses. A chi-squared or Fisher's exact test was used for categorical variables, and Student's t-test or a Mann Whitney U-test for quantitative data following an assessment of normality in a Kolmogorov-Smirnov test. Logistic regression analysis was performed to analyze the risk of acquiring SRSE. A p-value <0.05 indicated statistical significance.

## RESULTS

Of the 71 children enrolled in the study, 53.5% were male and the median age was 59 months (IQR, 22–115 months). Forty-five children had pre-existing epilepsy and 28.2% had been prescribed daily medications consisting of multiple antiepileptic drugs. **Tables 1 and 2** present the demographic data, antiepileptic medications, and seizure-triggering factors. The major cause of seizure was fever in 45.1% (CNS infections confirmed by spinal fluid investigations in 16.9% and infections other than CNS in 28.2%), withdrawal of antiepileptic medications in 40.9%, intoxication in 12.7% of children and intracranial hemorrhage due to arteriovenous malformation in one patient (1.4%). The median onset of seizure until PICU admission was 20 (IQR, 12.5–30) minutes. The initial work-up of metabolic status revealed hypoglycemia in 23.9%, hypocalcemia in 18.3%, hyponatremia in 15.5%, acidosis in 35.2%, and an elevated lactate level in 25.4% of the patients. Three (4.2%) patients died due to secondary complications of seizure. Fever at the initial onset of seizure occurred in 45.1% of the study population and more often in younger children (p=0.023). The

**Table 2. Triggering Factors and Anticonvulsive Medications of the study population.**

Seizure triggering factor	
Medication withdrawal	29 (40.9%)
Seizures with fever	32 (45.1%)
<i>Meningitis/encephalitis</i>	12 (16.9%)
<i>Infection not involving central nervous system</i>	20 (28.2%)
Intoxicity	9 (12.7%)
Intracranial hemorrhage*	1 (1.4%)
Anti-seizure medications of epileptic children	
Multi-drug anticonvulsive medications	20 (28.2%)
Levetiracetam	24 (33.8%)
Valproic acid	18 (25.4%)
Phenobarbital	11 (15.5%)
Carbamazepine	2 (2.8%)
Oxcarbamazepine	6 (8.5%)
Clonazepam	3 (4.2%)
Vigabatrin	3 (4.2%)
Lamotrigine	1 (1.4%)
Topiramate	1 (1.4%)
Clobazam	6 (8.5%)

\*Hemorrhage due to arteriovenous malformation

**Table 1. Demographics and clinical outcome based on fever.**

n (%)	Overall (71)	Seizure with fever (n=32)	Seizure without fever (n=39)	P
Age (months) *	59 (22-115 )	40 (23 - 112 )	63 (7 – 168)	<b>0.023</b>
Weight (kg) *	15 (9.5 – 28.0)	15 (10 - 31)	15.5 (8.4 – 28.7)	0.989
Male gender	38 (53.5%)	19 (59.4%)	19 (48.7%)	0.370
Sibling death	11 (15.5%)	6 (18.8%)	5 (12.8%)	0.359
The underlying condition	48 (67.6%)	25 (78.1%)	23 (59%)	0.086
Neurological etiology (other than epilepsy)	22 (31%)	12 (48%)	10 (43.5%)	
Metabolic	8 (11.3%)	4 (16%)	4 (17.4%)	
Cardiac	4 (5.6%)	3 (12%)	1 (4.3%)	
Chronic lung disease	2 (2.8%)	2 (8%)	-	0.494
Malignancy	1 (1.4%)	1 (4%)	-	
Hematological	1 (1.4%)	-	1 (4.3%)	
Immune deficiency	1 (1.4%)	-	1 (4.3%)	
Endocrinologic	7 (9.9%)	2 (8%)	5 (21.7%)	
Renal	2 (2.8%)	1 (4%)	1 (4.3%)	
Previous hospitalization	59 (83.1%)	28 (87.5%)	31 (79.5%)	0.370
History of epilepsy	45 (63.4%)	17 (53.1%)	28 (71.8%)	0.104
Multi-drug seizure medica- tion	20 (28.2%)	7 (21.9%)	13 (33.3%)	0.286
Number of seizures prior to ICU admission*	2 (1 - 4)	3 (1 - 4.5)	2 (1 - 3)	0.219
Length of seizures prior to ICU admission ( <i>minutes</i> )*	20 (12.5 - 30)	20 (15 – 37.5)	22.5 (10 – 30)	0.686
<b>PICU follow-up</b>				
Hyponatremia	11 (15.5%)	6 (18.8%)	5 (12.8%)	0.359
Hypoglycemia	17 (23.9%)	8 (25%)	9 (23.1%)	0.850
Hypocalcemia	13 (18.3%)	7 (21.9%)	6 (15.4%)	0.482
Metabolic acidosis	25 (35.2%)	6 (18.7%)	19 (48.7%)	<b>0.027</b>
Elevated lactate	18 (25.4%)	8 (25.0%)	10 (25.6%)	0.951
Midazolam infusion	28 (39.4%)	15 (46.9%)	13 (33.3%)	0.245
Sodium-Pentothal infusion	12 (16.9%)	6 (18.8%)	6 (15.4%)	0.707
<b>EEG monitoring</b>				
Abnormality of back- ground activity	17 (23.9%)	6 (18.75%)	11 (28.2%)	0.539
Epileptic abnormality	44 (62.0%)	21 (65.6%)	23 (58.9%)	0.515
Burst supression	12 (8.5%)	6 (18.8%)	6 (15.4%)	0.707
Focal epileptic abnormality	22 (31.0%)	10 (32.3%)	12 (30.8%)	0.894
Generalized epileptic abnormality	16 (22.5%)	8 (25%)	8 (20.5%)	0.653
Neuroimaging	26 (36.6%)	8 (25%)	18 (46.2%)	0.627
Abnormality at neuroim- aging	16 (22.5%)	7 (21.8%)	9 (23.1%)	0.185
<b>Outcome</b>				
PRISM-3 score *	1 (1-5)	1 (1 - 5)	1 (1 - 5)	0.459
Endotracheal intubation	28 (39.4%)	12 (37.5%)	16 (41%)	0.762
Tracheostomy	5 (7.0%)	4 (12.5%)	1 (2.6%)	0.123
Gastrostomy	10 (14.1%)	7 (21.9%)	3 (7.7%)	0.086
Length of PICU stay (days)*	7 (6 - 10)	7 (6 - 10.75)	7 (5 - 9)	0.608
Length of hospitalization (days)*	12 (11 - 13)	12 (11 - 13)	12 (11 - 13)	0.598
Mortality	3 (4.2%)	2 (6.3%)	1 (2.6%)	0.425

\*median (interquartile range)

demographic features and underlying chronic conditions were mostly similar between children with and without fever (**Table 1**). Fifteen (46.9%) children with fever required intravenous midazolam infusions and six (18.8%), received thiopental-sodium infusions to induce a burst-suppression pattern. As neurological complication, inability to tolerate airway maneuvers necessitated tracheostomy cannulation in 12.5% of the patients.

**Table 3** summarizes the demographic features and clinical outcomes of new-onset seizures. Epileptic children were older and more likely to have a history of sibling death ( $p=0.023$  and  $p=0.036$ , respectively), whereas a neuroimaging abnormality was detected in 57.5% of patients with a new-onset seizure ( $p=0.034$ ). These patients also had a significant elevation of the lactate level and acidosis and more frequently required invasive respiratory support ( $p=0.017$ ,  $p=0.002$ , and  $p=0.008$ , respectively), even if the duration and frequency of seizures were similar between the two groups ( $p=0.194$  and  $p=0.880$ , respectively).

In 12 children (16.9%), prolonged seizures progressed to SRSE and necessitated thiopental-sodium infusion (**Table 4**). Fever occurred in 50% of the SRSE patients with viral encephalitis (herpes simplex in two children; the cause of infection could not be identified in the third patient). The withdrawal of antiepileptic medication was defined as the second-most common etiology (33.3%). Two adolescents suffered SRSE due to multidrug abuse of tricyclic antidepressants and amphetamine overdose. Seizure duration prior to PICU admission was significantly longer in children with SRSE (median, 30 min; IQR, 23.75–60 min;  $p=0.002$ ). Low serum sodium (OR, 10.800; 95% CI, 2.518–46.318) and calcium levels (OR, 4.554; 95% CI, 1.159–17.892) were associated with SRSE development (**Table 5**); however, in the multivariate regression model, which included fever, new onset of disease, hyponatremia, hypocalcemia, hypoglycemia, and the PRISM-3 score, only the PRISM-3 score was identified as the independent risk factor for progressing to SRSE (OR, 1.174; 95% CI, 1.039–1.327;  $p=0.010$ ).

## DISCUSSION

In pediatric patients, SE is a common, life-threatening neurological emergency<sup>(19)</sup> often requiring intensive

care management. Moreover, the development of secondary complications, especially infection, the need for endotracheal intubation, and anticonvulsive drug-related adverse effects, may lead to increased morbidity and mortality. The goal of therapy with anticonvulsive medications is to terminate the seizure as early as possible, before the development of irreversible brain damage. Thus, the ability to predict which patients will progress to SRSE and thereby initiate timely preventive measures is of paramount importance. Our study investigated children with prolonged seizure who were admitted to one of the largest referral PICUs in Anatolia, Turkey. The major findings of this descriptive study were: i) anticonvulsive drug withdrawal and infections other than those involving CNS were the main seizure-triggering factors (40.9% and 28.2%, respectively), ii) seizure with fever occurred in 45.1% of the study population and at a younger age (median, 40 months); iii) children with new-onset seizure exhibited significant hemodynamic abnormalities, mostly an elevated lactate level and acidosis, iv) patients with a history of epilepsy were older and had a history of sibling death; v) low serum sodium and calcium levels were associated with SRSE and vi) the PRISM-3 score was the sole independent risk factor for progression to SRSE (OR, 1.174; 95% CI, 1.039–1.327).

Among the risk factors for SE morbidity (age, etiology, and duration of seizure), etiologic factors have the utmost importance<sup>(1,20-23)</sup>. The incidence rates of SE in epileptic children ranges from 34% to 53.3%<sup>(24,25)</sup>. The percentage of epileptic children in our study was slightly higher (63.4%), and drug withdrawal was identified as the major determinant of prolonged seizure in these patients (40.9%). In a study of children with new-onset seizure, fever was the most prevalent cause (57.7%). Lacroix et al. reported similar findings regarding seizure etiology as an epilepsy background in 45.6% of their study population and febrile seizure was the most frequent cause of SE<sup>(25)</sup>. In another study based on a large dataset derived from 13 hospitals, febrile seizures were detected in 12% of 1679 hospital admissions<sup>(26)</sup>.

Similar to the results of previous studies, sex was not a determining factor despite the higher percentage of males in our study population (female-to-male ratio, 1:1.15)<sup>(27,28)</sup>. Previous reports on SE included patients

Table 3. Demographics of new-onset seizures

n (%)	Overall (n=71)	Epilepsy history (n=32)	New onset of seizure (n=39)	p
Age (months) *	59 (22-115)	63 (20.5 – 122.5)	40.5 (22.75 – 98.50)	<b>0.023</b>
Weight (kg) *	15 (9.5 – 28.0)	15 (8.9 – 26.25)	16 (10.25 – 36.50)	0.989
Male gender	38 (53.5%)	25 (55.6%)	13 (50.0%)	0.651
Death of a Sibling	11 (15.5%)	10 (22.2%)	1 (3.8%)	<b>0.036</b>
The underlying conditions	48 (67.6%)	25 (55.6%)	23 (88.5%)	<b>0.004</b>
Neurologic (other than epilepsy)	22 (31%)	14 (56%)	8 (34.8%)	
Metabolic	8 (11.3%)	5 (20%)	3 (13%)	
Cardiac	4 (5.6%)	1 (4%)	3 (13%)	
Chronic lung disease	-	3 (8.7%)	-	0.214
Malignancy	1 (1.4%)	1 (4%)	-	
Hematological	1 (1.4%)	-	1 (4.3%)	
Immune deficiency	1 (1.4%)	-	1 (4.3%)	
Endocrinologic	7 (9.9%)	2 (8%)	5 (21.7%)	
Renal	2 (2.8%)	-	2 (4.2%)	
Previous hospitalization	59 (83.1%)	37 (82.2%)	22 (84.6%)	0.536
Multi-drug anticonvulsive medication	20 (18.3%)	20 (44.4%)	-	-
No. of seizure prior to ICU admission*	1 (1-3)	1 (1 - 3)	1 (1 - 2)	0.880
Duration of seizure prior to ICU (minutes)*	20 (12.5 - 30)	20 (10 – 30)	27.5 (16.25–56.25)	0.194
Seizure triggering factor				
Medication withdrawal	29 (40.9%)	29 (64.4%)	-	-
Fever	32 (45.1%)	17 (37.8%)	15 (57.7%)	0.496
Meningitis/encephalitis	12 (16.9%)	7 (15.6%)	5 (19.2%)	0.464
Infections not involving CNS**	20 (28.2%)	10 (22.2%)	10 (38.5%)	0.143
Toxicity	9 (12.7%)	-	9 (34.6%)	-
Intracranial hemorrhage	1 (1.4%)	-	1 (3.8%)	-
PICU follow-up				
Hyponatremia	11 (15.5%)	7 (15.6%)	4 (15.4%)	0.633
Hypoglycemia	17 (23.9%)	9 (20%)	8 (30.8%)	0.306
Hypocalcemia	13 (18.3%)	11 (24.4%)	2 (7.7%)	0.071
Metabolic acidosis	25 (35.2%)	5 (19.2%)	20 (44.4%)	<b>0.008</b>
Elevated lactate	18 (25.4%)	5 (11.1%)	13 (54.1%)	<b>0.002</b>
Midazolam infusion	28 (39.4%)	20 (44.4%)	8 (30.8%)	0.256
Sodium-Pentothal infusion	12 (16.9%)	8 (17.8%)	4 (15.4%)	0.536
EEG monitoring				
Abnormal background activity	17 (23.9%)	12 (26.6%)	5 (19.2%)	0.648
Epileptic abnormality	44 (62.0%)	33 (73.3%)	11 (42.3%)	0.104
Burst suppression	12 (16.9%)	8 (17.8%)	4 (15.4%)	0.536
Focal epileptic abnormality	22 (31.0%)	14 (31.8%)	8 (30.8%)	0.927
Generalized epileptic abnormality	16 (22.5%)	13 (28.9%)	3 (11.5%)	0.092
Neuroimaging	26 (36.6%)	12 (26.6%)	14 (53.8%)	<b>0.034</b>
Abnormality at neuroimaging	16 (22.5%)	11 (24.4%)	5 (19.2%)	0.567
Outcome				
PRISM-3 score*	1 (1-5)	1 (1 – 5)	1 (1 – 5.25)	0.593
Endotracheal intubation	28 (39.4%)	13 (28.9%)	15 (57.7%)	<b>0.017</b>
Tracheostomy	5 (7.0%)	3 (6.7%)	2 (7.7%)	0.609
Gastrostomy	10 (14.1%)	7 (15.6%)	3 (11.5%)	0.464
Length of PICU stay (days)*	7 (6 - 10)	7 (6 – 11)	6 (5 – 7.25)	0.201
Length of hospitalization (days)*	12 (11 - 13)	12 (11 – 13)	12 (10.75 – 13)	0.573
Mortality	3 (4.2%)	1 (2.2%)	2 (7.7%)	0.301

\*median (interquartile range), \*\* CNS: central nervous system

ranging in age from 1 to 6.5 years<sup>(25,28,29)</sup>, whereas the median age of SE children in our study was 59 months (IQR, 22–115 months). In the group with febrile SE, the median age was lower, 40 months. Because younger children are more susceptible to infections, febrile SE has a tendency to occur at younger ages (40 vs. 63 months for epileptic children,  $p=0.023$ ). Thus, our finding regarding the older age of children with febrile SE is in contrast to those of previous investigations in which the age range was 14–23 months<sup>(8,20,30-36)</sup>. This discrepancy may reflect socio-cultural differences in early childhood education and care. According to the 2019 Organization for Economic Cooperation and Development (OECD) report, early childhood education and care in children aged 0–2 years is provided at a rate of 1% in Turkey, a much lower rate than in other OECD countries, where it is as high as 60%<sup>(37)</sup>. In Turkey, caring for children at home by a parent or an elderly relative is much more common, such that the risk of encountering infections and febrile SE at a younger age is reduced.

Few studies have investigated the effect of seizure on metabolism<sup>(38)</sup>. Lactate is the end-product of anaerobic glycolysis. In cellular hypoxia, an adaptive process emerges to generate energy but at the cost of worsening acidosis and the degradation of pyruvate to lactate<sup>(39)</sup>. Hypoxia also explains why lactate elevation occurs in tonic-clonic seizures, during which catecholamines are discharged and metabolic alterations in muscle contribute to lactate elevation. Matz et al. reported significantly increased lactate levels during generalized tonic-clonic seizures and suggested that lactate levels during seizures could be used to distinguish psychogenic non-epileptic and syncopal events<sup>(38)</sup>. Our findings provide support for this hypothesis, as the metabolic state was altered in our patients with prolonged seizure, including metabolic acidosis (35.2%) and lactate elevation (25.4%). Interestingly, although the seizure duration prior to PICU admission was similar between children with a new-onset seizure and epileptic patients, significant metabolic abnormalities in the form of lactate elevation ( $p=0.002$ ) and acidosis ( $p=0.008$ ) were detected in the new-onset seizure patients via initial blood gas analysis. Moreover, these patients more often required invasive respiratory support. Neurophysiological studies are needed to determine whether this condition is a coincidence or a hemostatic adaptation. Nonetheless, anyone experiencing seizure, regardless of the epileptic background, should be closely

monitored and treated accordingly.

Acute metabolic disturbances of glucose, calcium, and sodium may lead to recurrent or prolonged seizures<sup>(40,41)</sup>. If left untreated, they can result in permanent brain tissue injury<sup>(18)</sup>. Clinical and experimental studies have shown that hyponatremia is a triggering factor in convulsion<sup>(42-44)</sup>. In a child manifesting an afebrile seizure, the American Academy of Neurology recommends screening for electrolyte anomalies, especially hyponatremia, which is a common cause of acute afebrile seizure in children<sup>(45)</sup>. A patient is considered hyponatremic if the serum sodium level is  $<135$  meq/L, and severely hyponatremic if the level is  $<125$  meq/L<sup>(18)</sup>. Brain swelling and seizures related to a low sodium level are more likely to develop if the level falls to 115 meq/L. However, a patient with electrolyte disturbances at acute onset is more likely to develop seizures. However, defining the absolute levels of electrolyte abnormality likely to induce seizure is difficult<sup>(46)</sup>. Moreover the larger brain-to-skull size ratio makes children more prone to developing symptomatic hyponatremia<sup>(18)</sup>. In the current study, patients were considered hyponatremic if the serum sodium level was  $<135$  meq/L. According to the univariate analysis, following the initiation of a seizure, a decrease in the serum sodium level less than 135 meq/L increases the odds of developing SRSE 10.8-fold. How hyponatremia triggers a seizure could not be further investigated, because laboratory data were obtained only after PICU admission and not before. However, low sodium levels may increase the risk of continuing seizure, thus leading to SRSE progression, even in cases with hyponatremia ( $\text{Na} <135$  meq/L). The results of our study are concordant with those of a previous study of children with gastroenteritis and seizure, who found that even mild hyponatremia ( $\text{Na} = 126\text{--}134$  meq/L) can affect the duration of seizure and thereby, increase the risk of SE<sup>(47)</sup>. By contrast, Holtkamp et al. reported that low sodium levels cannot be the sole factor initiating seizure even if patients with RSE frequently experience hyponatremia (serum sodium level  $<135$  meq/L) compared to those with non-RSE<sup>(48)</sup>. Another study has also reported that low sodium levels are not related to seizure alone, but it occurs as a consequence of thiopental infusion due to drug-related volume-dependent antidiuretic hormone secretion<sup>(49)</sup>. In critically ill children, excessive secretion of arginine vasopressin results in free water retention, and the risk of hyponatremia can be exacerbated by the administration

Table 4. Demographics and clinical outcomes of super-refractory SE

N (%)	Super-refractory SE (n=12)	Seizures (n=59)	p
Age (months) *	69 (19.5 – 149.75)	50 (22 – 103)	0.771
Weight (kg) *	16 (10.5 – 28)	15 (9.125 – 30)	0.644
Male gender	8 (66.7%)	30 (50.8%)	0.317
Sibling death	4 (33.3%)	7 (11.9%)	0.082
The underlying conditions	7 (58.3%)	41 (69.5%)	0.332
Neurological	4 (57.1%)	18 (43.9%)	
Metabolic	3 (42.9%)	5 (12.2%)	
Cardiac	-	4 (9.8%)	
Chronic lung disease	-	2 (4.9%)	0.085
Malignancy	-	1 (2.4%)	
Hematological	-	1 (4.3%)	
Immune deficiency	-	1 (2.4%)	
Endocrinologic	-	7 (17.1%)	
Renal	-	2 (4.9%)	
Previous hospitalization	11 (91.7%)	48 (81.4%)	0.350
Previous epilepsy history	8 (66.7%)	37 (62.7%)	0.536
Duration of seizure prior to ICU admission	30 (23.75 – 60)	15 (10 – 30)	<b>0.003</b>
Abnormality at neuroimaging	5 (83.3%)	7 (33.3%)	<b>0.002</b>
Multi-drug epilepsy medication	5 (41.7%)	15 (25.4%)	0.212
Levetiracetam	5 (41.7%)	19 (32.2%)	0.375
Valproic acid	3 (25%)	15 (25.4%)	0.643
Phenobarbital	3 (25%)	8 (13.6%)	0.272
Carbamazepine	1 (8.3%)	1 (1.7%)	0.831
Oxcarbamazepine	2 (16.7%)	4 (6.8%)	0.266
Clonazepam	2 (16.7%)	1 (1.7%)	0.072
Vigabatrin	1 (8.3%)	2 (3.4%)	0.431
Lamotrigine	-	1 (1.7%)	0.831
Topiramate	-	1 (1.7%)	0.831
Clobazam	1 (8.3%)	5 (8.5%)	0.734
<b>Triggering factors</b>			
Medication withdrawal	4 (33.3%)	25 (342.4%)	0.403
Fever	6 (50%)	27 (45.8%)	0.474
CNS infection	3 (25%)	9 (15.3%)	0.326
Infections not involving CNS	3 (25%)	17 (28.8%)	0.547
Toxicity**	2 (16.7%)	7 (11.9%)	0.474
Intracranial hemorrhage	-	1 (1.7%)	-
<b>PICU follow-up</b>			
Hypoglycemia	2 (16.7%)	15 (25.4%)	0.408
Hypocalcemia	5 (41.7%)	8 (13.6%)	<b>0.036</b>
Hyponatremia	6 (50%)	5 (8.5%)	<b>0.002</b>
Metabolic acidosis	6 (50%)	19 (32.2%)	<b>0.014</b>
Lactate elevation	7 (58.3%)	11 (18.6%)	<b>0.008</b>
<b>Outcome</b>			
PRISM-3 score *	10 (1.25 – 14.75)	1 (1 – 4)	<b>0.003</b>
Tracheostomy	2 (16.7%)	3 (5.1%)	0.196
Length of PICU stay (days) *	24 (15.5 – 27.5)	6 (5 – 8)	<b>&lt; 0.001</b>
Length of hospitalization (days)*	33 (25.75 – 48.75)	11 (11-12)	<b>&lt; 0.001</b>
Mortality	3 (25%)	-	NA

\*median (interquartile range),\*\* toxicity: multi-drug abuse of tricyclic antidepressants and amphetamine overdose

**Table 5. Univariate logistic regression model for super-refractory status epilepticus.**

	95% CI			
	Odds Ratio	Lower limit	Upper Limit	p
<b>Fever</b>	1.269	0.366	4.398	0.707
<b>New- onset seizure</b>	0.841	0.227	3.120	0.796
<b>Hyponatremia</b>	10.800	2.518	46.318	<b>0.001</b>
<b>Hypocalcemia</b>	4.554	1.159	17.892	<b>0.030</b>
<b>Hypoglycemia</b>	0.587	0.115	2.986	0.521
<b>PRISM-3 score</b>	1.213	1.066	1.379	<b>0.003</b>

of hypotonic fluids. Therefore, since the early 2000s, the administration of isotonic fluids in the form of saline (0.09% NaCl solution) and dextrose has been recommended as maintenance fluid therapy<sup>(45-47)</sup>. Again, we recommend that health-care providers supply isotonic solutions to convulsive children, unless medically indicated, as maintaining serum sodium levels within a normal range is crucial to terminating the seizure as early as possible.

Critically-ill children requiring intensive care often exhibit abnormal EEG features, an increased risk of seizure, and neurological deterioration<sup>(50)</sup>. Seizure is also observed as one of the short-term outcomes in very sick children<sup>(51)</sup>. The PRISM-3 score predicts the risk of mortality in children, based on the severity of illness according to abnormalities in 17 physiological variables as assessed via physical examination and laboratory tests within 24 hs of intensive care unit admission<sup>(52)</sup>. In our study the multivariable logistic regression analysis identified the PRISM-3 score as the sole independent risk factor for progressing to SRSE, but this finding must be interpreted cautiously because the score is calculated from values recorded on the first day of intensive care unit admission, which are likely to be the worst. Future studies should determine whether the PRISM-3 score is a predictor of SRSE or reflects life-threatening multiorgan system dysfunction as a result of ongoing seizure.

Seizure persisting for >24 h after the onset of anesthesia is referred to as SRSE and includes seizure recurrence following a reduction or withdrawal of anesthesia<sup>(53)</sup>. The most common etiology is a history of epilepsy and the development of immune-mediated encephalitis<sup>(16)</sup>. In our study, 28 children (39.4%) received midazolam infusions (initial dose, 0.1–1 mg/kg/h), 12 of whom (16.9%) progressed to SRSE despite increased doses of

midazolam, and these children subsequently required sodium thiopental infusions. Burst-suppression patterns were observed in the intermittent EEG recordings. Eight of these children had refractory epilepsy and had been receiving multiple antiepileptic medications. In four of them, drug withdrawal was the main cause of prolonged seizure, and the other four had new-onset seizures, including two patients with herpes simplex encephalitis. The underlying etiology could not be identified despite testing for autoimmune diseases.

Neuroimaging was performed in 26 children (36.6%) within the first day of hospital admission. Abnormalities were detected in 22.5% but none required surgical intervention. In the study by Sadik et al., 72% of the patients underwent neuroimaging, with abnormalities detected in 22.8% of them<sup>(54)</sup>. In the series of Şahin et al., 20 of 45 convulsive patients underwent CT imaging, and 55% had abnormalities, while 23 patients were examined using cranial MRI, with pathological findings detected in 78.2% of them<sup>(55)</sup>. The scanning rate of neuroimaging in the present study was far less than relative to those two studies. This difference can be explained by the epileptic profile of the study population, as in our patients the most common cause of seizure was the withdrawal of anti-epileptic drugs, which reduced the necessity of diagnostic neuroimaging.

Three children died of secondary complications (4.2%), consistent with the rates reported in previous studies, which varied from 3.4% to 11% (56,57). In Specchio et al., the mortality rate was 3.5% in patients in the acute phase of SE and 4.04% during follow-up. The authors found no evidence of a relationship between age at onset, duration of seizure, and mortality but suggested that mitochondrial disease, cerebral hemorrhage, and CNS malignancies were associated with higher mortality rates<sup>(57)</sup>.

Our study had several limitations. First, its retrospective design led to a risk of bias. Second, it was performed in a single center with a small number of patients. Both aspects limit the drawing of general conclusions based on the determined outcomes. Third, the study period was restricted to the PICU stage and did not include the pre-intensive care period. However, our hospital has a level-III, high-volume-referral intensive care unit serving a densely populated region, such that the patients were likely to have been representative of a larger pediatric population with SE. Because all patients with prolonged seizures are transferred to our unit, the clinico-epidemiologic profile of this population could be analyzed in detail.

## CONCLUSION

Prolonged seizures and SE are life-threatening conditions if not immediately treated. Close monitoring is crucial in patients who present with electrolyte imbalances because hyponatremia and hypocalcemia are risk factors for developing SRSE. Therapeutic management consists of timely intervention with anticonvulsive medication and taking the measures necessary to prevent metabolic disturbances.

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