EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2022.68916
Eurasian J Emerg Med. 2023;22(2): 71-81

Determining Prevalence and Risk Factors of Seizure Recurrence in the Early Period in Patients Who Present to the Emergency Department with Epileptic Seizures

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Abstract

Aim: Although the basic principles of acute epileptic seizure management in the emergency department (ED) are well known, there is no consensus on the optimal discharge time from the ED for patients who return to a normal-basal state of consciousness after an epileptic seizure. The main concern for physicians in terms of the optimal discharge time from the ED is the possibility of acute recurrent seizures (ARS) in the early postdischarge period. Such concerns can lead to extended monitoring of patients, resulting in overcrowding in the ED and higher hospital charges. The aim of this study was to determine the frequency of ARSs and risk factors for recurrence within the first 6 and 24 h after presentation to the ED with an acute seizure in patients with a confirmed diagnosis of epilepsy.

Materials and Methods: This prospective observational study was conducted with patients aged older than 18 year old with a diagnosis of epilepsy who presented with convulsive seizures to the ED between October 2018 and October 2019. The primary outcome was the frequency of ARS within the early period (6 and 24 hours). The second outcome was the potential risk factor for ARS, which was seizure recurrence within the first 6 or 24 h after admission to the ED with the complaint of a seizure.

Results: In to patients with epilepsy with seizure attacks were included during the study period. The prevalence of ARS within the first 6 and 24 h was found to be 21.8% and 27.4%, respectively. Risk factors for ARS within 6 h were found to be non-adherent to antiepileptic drug (AED) therapy, active seizures/postictal period on admission, and white blood cells, while risk factors for ARS within 24 h were found to be non-adherent to AED therapy, AED polytherapy, a history of weekly seizures, duration of the postictal period, and white blood cells.

Conclusion: ARS are not rare in the early period after admission to the ED, with an incidence of 21.8% in the first 6 h and 27.4% in the first 24 h. Potential risk factors of ARS seem to be non-adherent to AED therapy, AED polytherapy, a history of weekly seizures, duration of the postictal period, and white blood cell.

Keywords: Acute recurrent seizure, acute repetitive seizure, seizure cluster, epilepsy, emergency department

Introduction

Patients with a history of epilepsy often experience acute seizures and m, andof these patients are admitted to the emergency department (ED) for treatment (1). Although the basic principles of acute epileptic seizure management in the ED are well known, there is no consensus on the optimal discharge time from the ED for patients who return to a normal-basal state of consciousness after an epileptic seizure (2,3). The main concern for physicians in terms of the optimal discharge time from the ED is the possibility of acute recurrent seizures (ARS) in the early post-discharge period (i.e., within the first 24 hr), as ARS in the early post-discharge period may be associated with an increased risk of status epilepticus, morbidity, mortality, and re-admission to the ED (4-7). Such concerns can lead to extended monitoring of patients, resulting in overcrowding in the ED and higher hospital

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Cite this article as: Şencanlar Çetiner H, Çorbacıoğlu ŞK, Yazıcıoğlu Cezayir D, Emektar E, Çevik Y. Determining Prevalence and Risk Factors of Seizure Recurrence in the Early Period in Patients Who Present to the Emergency Department with Epileptic Seizures. Eurasian J Emerg Med. 2023;22(2): 71-81.

Received: 28.02.2022
Accepted: 27.04.2022

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charges. Determining the risk factors for ARS can shed light on patients who require long-term monitoring. Such information is crucial for both physicians and patients.

Although several studies have determined the prevalence of ARS and associated risk factors, there is no clear consensus in the literature on this issue. The use of different terminologies for ARS is one of the main reasons for the lack of consensus (4,8). Although seizure cluster (SC) is generally used to identify ARS, it is not listed in the International League against Epilepsy (ILAE) Commission on Classification and Terminology (9). Similarly, there are different clinical definitions for SC, with some studies defining it as three or more seizures in 24 h (10-12), and others defining it as two to four seizures in less than 48 h (13), two or more seizures in 6 h (14), or two or more seizures in 24 h (15). Due to these diverse definitions of SC in the literature, different studies have reported different risk factors and prevalences. Consequently, no clear clinical consensus has been established.

The aim of this study was to determine the frequency of ARS and risk factors for recurrence within the first 6 and 24 h after presentation to the ED with an acute seizure in patients with a confirmed diagnosis of epilepsy.

Materials and Methods

Study Type and Design

This single-center prospective study was conducted in the ED of a Ankara Keçiören Training and Research Hospital between 15 October 2018 and 15 October 2019 after receiving approval from the Local Ethics Committee (protocol id and date: 48865165-020/07.10.2018). The research was conducted in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all patients or their legally authorized relatives.

Subjects

During the study period, all consecutive patients aged older than 18 year old with a diagnosis of epilepsy who presented with convulsive seizures (generalized type according to the ILAE 2017 classification) to the ED were included in the study. Patients who were pregnant, who were diagnosed with status epilepticus at the time of admission, and who had a lack of basic laboratory results (hemogram, biochemistry panel, venous blood gases) or clinical/demographic data were excluded from this study.

Study Protocol

All patients included in the study were evaluated and examined by emergency physicians in a critical care room of the ED at the time of admission. Patients' demographic and clinical data, vital signs, physical/neurological examination findings, bedside blood sugar, and main laboratory findings, including those of a hemogram, biochemistry panel, and venous blood gases, and pregnancy tests were obtained and recorded by the emergency physicians. Toxicology screening and radiological examination were performed if clinically indicated. Details on each patient's epilepsy history and previous and most recent seizure attacks were obtained from patients, their relatives, and other eyewitnesses. These data included a history of epilepsy in the patient's family, patients' sleep patterns/sleep disorders, type and frequency of previous seizures, epilepsy patterns and seizure recovery times, signs and symptoms during the postictal period, seizure-triggering clinical conditions, and whether antiepileptic drug (AED) use is regular or not (adherent or non-adherent therapy) - non-adherent to AED therapy was defined as non-use of three or more days in the last month based on the anamnesis of the patient.

After initial supportive care and resuscitative procedures when required, all patients were observed for at least 6 h in the ED according to routine clinical practice in our hospital. After this observation period, patients without repeated seizures or clinical conditions requiring hospitalization and did not require specific treatment were discharged from the ED. All these patients were asked to return to the ED within a 24-h period from the time of discharge from the ED to undergo screening by a neurologist in the neurology clinic. If clinically indicated, the neurologist performed electroencephalographic testing. At the same time, the patient was asked about recurrent seizures in the 24-h period since their first admission to the ED. Finally, the neurologist categorized the epileptic seizure according to the ILAE 2017 classification. Patients with seizures other than generalized seizures (focal and unknown) and those who were not followed up were excluded.

Outcomes of Interest

Two outcomes were defined in this study. The first outcome was the frequency of ARS in patients with a confirmed diagnosis of epilepsy who presented to the ED with acute seizures in the early period (i.e., within the first 6 h and 24 hr). The second outcome was the potential risk factors for ARS. In this study, ARS was defined as seizure recurrence within the first 6 or 24 h after admission to the ED with the complaint of a seizure (14,16).

Statistical Analysis

All data were analyzed using Statistical Package for the Social Sciences (SPSS) v25.0 for Mac OS X (SPSS Inc., Chicago, IL, USA). The normality of the data distribution was determined by the Shapiro-Wilk test, histograms, and Q-Q plots. The categorical variables of the patients were expressed as numbers and percentages and analyzed using a chi-square test. Continued variables were

presented as the mean standard deviation or median values and interquartile range (IQR) of 25-75%. Non-parametric values were analyzed using the Mann-Whitney U test, and parametric values were analyzed using the Student's t-test. To determine the predictive value of the variables, those with a p value of <0.1 in the univariate analysis were entered into a multivariate regression model using the blockwise entry method. Correlations among these variables were analyzed using Spearman's test. In each pair, the variable that detected a correlation with the other variable was excluded from the regression model. To assess the model's goodness of fit, the Hosmer-Lemeshow test was performed. The 95% confidence intervals (95% CIs) were calculated whenever appropriate, and a two-tailed p value of <0.05 was considered statistically significant.

Results

In to patients with epilepsy with seizure attacks were included during the study period. The median age of the patients was 31.5 years (IQR: 25-75%: 24-43), and 72 (50.7%) of the patients were males. At the time of admission to the ED, 54 (38%) of the patients were in the postictal period/active seizure and the remaining 88 (62%) patients were fully conscious. According to the history taken from the patients' relatives, the postictal period was prolonged in 35 (24.6%) of the patients as compared to the usual duration. The baseline characteristics of the patients are shown in Table 1.

Thirty-one (21.8%) of the 142 patients experienced ARS within the first 6 h of follow-up in the ED. When the demographic and clinical characteristics of these patients were compared with those without ARS during this period, the following factors were more common in the ARS group: cerebral palsy, a weekly history of seizures, active seizures or postictal period on admission to the ED, psychotropic drug use in the last 24 h, and intravenous AED administration in the ED. In addition, the duration of the postictal period and lactate and white blood cell values on admission was higher in patients with ARS than in those without ARS. The GCS and pH values of patients with ARS were lower than those without ARS. In the multivariate regression model created to assess the factors predicting ARS within the first 6 h of follow-up in the ED, nonadherent to AED therapy [odds ratio (OR): 2.5, 95% CI: 1.01 to 6.4], active seizures/postictal period on admission (OR: 4.3, 95% CI: 1.7 to 11), and white blood cell (OR: 1.2, 95% CI: 1.08 to 1.3) were predictive factors for ARS within the first 6 h of follow-up in the ED (Table 2).

In terms of the prevalence of ARS and associated risk factors within the first 24 h after admission to the ED, 39 of the 142 (27.4%) patients experienced ARS within this period. When the demographic and clinical characteristics of the patients with and without ARS within the first 24 h after admission to the ED were compared, the following factors were more common in the ARS group: cerebral palsy, a history of cluster epilepsy, non-adherent to AED therapy, AED polytherapy, a history of weekly seizures, active seizures or postictal period on admission to the ED, psychotropic drug use in the previous 24 hr, and intravenous AED administration in the ED. In addition, the duration of the postictal period, pulse rate, length of stay in the ED, and lactate and white blood cell values on admission were higher in patients with ARS than in those without ARS. The GCS and pH values of the patients with ARS were lower than those without ARS. In the multivariate regression model created to assess the factors predicting ARS within the first 24 h after admission to the ED, non-adherent to AED therapy (OR: 2.5, 95% CI: 1.09 to 6.5), AED polytherapy (OR: 2.9, 95% CI: 1.08 to 8.1), a history of weekly seizures (OR: 3.9, 95% CI: 1.2 to 12), duration of the postictal period (OR: 1.01, 95% CI: 1.001 to 1.026), and white blood cell (OR: 1.18, 95% CI: 1.06 to 1.3) were predictive of ARS within the first 24 h after admission to the ED (Table 3).

Discussion

The pThisy investigated prevathe prevalence and factors for ARS or SC in patients with epilepsy who were admitted to the ED with the complaint of seizures. In this study, the prevalence of ARS after admission to the ED was 21.8% in the first 6 h and 27.4% in the first 24 h. Previous studies on the prevalence of ARS or SC reported figures ranging from 3% to 57% (9,16-18). The difference in the reported seizure prevalence may be due mainly to the lack of consensus on the definitions of SC and ARS, both of which are used to describe repetitive seizures in the early period. Among the various definitions of ARS, in this study, ARS was defined as having two or more seizures in the first 6 h (14) and two or more seizures in the first 24 h (16). We considered this definition more appropriate in emergency medicine practice in our study. In terms of ED practice and the first 6 h after an acute seizure, although there is no clear evidence, the general view is that all patients should be monitored during this period and that those without seizure recurrence during this time, as well as those who not have any significant clinical problems requiring specific treatment, can be discharged. Similarly, during this 6-h period, despite the lack of a high level of evidence, patients who have seizures again are considered to have a high risk of status epilepticus (7). Because of concerns about ARS, many patients are monitored for long periods in the ED. To address this issue, it is important to define the main risk factors for ARS in the first 6 to 24 h.

In this study, although several variables were identified as potential risk factors for ARS within the first 6 h in the univariate analysis,

Table 1. Demographical and clinical characteristics of all patients	
Gender n (%)	
Male	72 (50.7)
Female	70 (49.3)
Age median (IQR 25-75%)	31.5 (24-43)
Comorbidities n (%)	
Chronic hypertension	10 (7)
Coroner artery disease	6 (4.2)
Diabetes mellitus	6 (4.2)
Cerebral palsy	5 (3.5)
Cerebra-vascular event	8 (5.6)
Psychiatric disorders	16 (11.3)
Chronic alcohol use	11 (7.7)
Others	23 (16.2)
The history of epilepsy n (%)	
Epilepsy history in family	28 (19.7)
Previously meningitis history	6 (4.2)
Febrile convulsion history	41 (28.9)
Difficult birth history	25 (17.6)
Severe head trauma history*	35 (24.6)
Previously status epilepticus history	21 (14.8)
Hospital admission history due to epilepsy	48 (33.8)
ICU admission history due to epilepsy	17 (12)
Intubation history due to epilepsy	3 (2.1)
Epileptic surgery history	1 (0.7)
Cluster-type epilepsy history**	75 (52.8)
Drug history n (%)	
AED use	132 (93)
Nonadherent to AED therapy	48 (33.8)
Unused last of AED dosage	70 (49.3)
Polytherapy AED use	47 (33.1)
Third-generation AED use	91 (64.1)
Age of when diagnosed epilepsy median (IQR 25-75%)	20 (12-30)
Duration time since diagnosed epilepsy/year median (IQR 25-75%)	10 (3-20)
The presence of weekly routine seizures in history n (%)	22 (15.5)
The presence of monthly routine seizures in history n (%)	55 (38.7)
Epilepsy etiology n (%)	
Symptomatic#	93 (65.5)
Idiopathic##	49 (33.1)
The state of consciousness on admission to ED n (%)	
Active seizure/postictal period	54 (38)
Conscious	88 (62)
Duration of postictal period (minute) median (IQR 25-75%)	20 (10-40)
Seizure features n (%)	
Presence aura in the pre-seizure period	46 (32.4)
Prolonged postictal period***	35 (24.6)
Seizure period	
06:00-12:00	55 (38.7)
12:00-20:00	39 (27.5)
20:00-06:00	48 (33,8)
Relationship of seizure to sleep	
On sleeping	31 (21.8)
Awake	111 (78.2)
Clinical features n (%)	
Fever higher than 38 °C in last 24 h	23 (16.2)
Disturbed sleep in the last 48 h	79 (55.6)
Alcohol intake in the last 24 h	5 (3.5)
Acute traumatic injury	57 (40.1)
Psychotropic drug use in the last 24 h	7 (4.9)
Acute psychological stress in the last week	87 (61.3)
Changing AED dosage	21 (14.8)
Use of herbal medicine	4 (2.8)

Table 1. Continued	
Cerebral localization of epilepsy**** n (%)	
Frontal	9 (6.3)
Temporal	22 (15.5)
Parietal	49 (34.5)
Occipital	12 (8.5)
Limbic	5 (3.5)
Unknown	45 (31.7)
Vital signs on admission median (IQR 25-75%)	
Systolic blood pressure: mmHg	120 (110-133)
Diastolic blood pressure: mmHg	70 (65-78.25)
Pulse-beat/min	91.5 (79.75-102)
Fever -°C	36.4 (36.1-36.8)
Blood sugar: mg/dL	105 (91.75-121)
Oxygen saturation -%	96 (94-98)
Glasgow-coma scale	15 (11-15)
Laboratory findings median (IQR 25-75%)	
pH	7.38 (7.31-7.41)
PCO_2 - mmHg	40.5 (35-46)
Bicarbonate - mmol/L	23 (20-26)
Lactate - mEq/L	3.2 (1.9-6.3)
White blood cell - $x10^3/\mu L$	8.7 (6.8-11.5)
Neutrophil - $x10^3/\mu L$	4.95 (3.9-7.2)
Lymphocyte - $x10^3/\mu L$	2.4 (1.6-3.3)
Hemoglobin - g/dL	14.05 (12.8-15.5)
Platelet - $x10^3/\mu L$	239.5 (185.7-291)
Creatinine	0.7 (0.8-0.9)
Urea - mg/dL	24 (19-30)
BUN - mg/dL	10 (8-14)
ALT - IU/L	14 (11-22)
AST - IU/L	21 (17-27)
GGT - IU/L	24 (14.7-41.5)
Total bilirubin: mg/dL	0.3 (0.1-0.4)
Direct bilirubin - mg/dL	0.08 (0.05-0.1)
Sodium - mEq/L	138 (137-140)
Potassium - mEq/L	4 (3.8-4.3)
Calcium - mg/dL	9.55 (9.1-9.9)
Length of stay ED median (IQR 25-75%)	4 (4-6)
IV AED needing in ED n (%)	27 (19)

*Severe head trauma history: Presence of head trauma requiring hospitalization or surgical intervention and accompanying altered mental status in history.
**Cluster-type seizure: Two or more seizures in 24 h.
***Prolonged postictal period: Prolonged postictal period compared to the previous postictal period based on the anamnesis taken from relatives.
****Location detected on EEG that performed after the last seizure attack.
#Epilepsy disease secondary to organic lesion (intracranial hemorrhage, ischemic stroke, etc.).
##Epilepsy that starts unrelated to any organic lesion.

only the white blood cell count, non-adherent to AED therapy, and active seizures/postictal period on admission were significant risk factors in the multivariate logistic regression analysis. Similarly, when we assessed the risk of ARS within the first 24 h, a history of weekly seizures, AED polytherapy, non-adherence to AED therapy, white blood cell count, and postictal period duration were significant risk factors in the multivariate logistic regression analysis. Although small in number, several studies are focused on ARS prevalence and its potential risk factors in the literature. However, the main findings of these studies differ from each other. One possible reason for the discord be differences in the composition of the study populations.

In a prospective cohort study on 163 epilepsy patients older than 18 years, Haut et al. (12) aimed to determine the potential risk factors for SC, which they defined as the occurrence of three or more seizures within a 24 h period. In their study, in which generalized seizures were excluded, the authors reported that the prevalence of SC was 29% and that a history of head trauma with loss of consciousness before epilepsy onset and extratemporal lobe epilepsy were risk factors for SC. In another prospective cohort study on 300 epilepsy patients older than 12 years, Detyniecki et al. (14) reported that the number of AEDs used during a patient's lifetime was a risk factor for SC, which they defined as two or more seizures in a 6 h period. In their study, extratemporal lobe epilepsy was not a risk factor for SC (14). Another important finding of the study by Detyniecki et al. (14) was that the occurrence of SC in the previous year was a risk factor for the recurrence of SC the following year (OR:

Table 2. Demographical and clinical characteristics of patients according to the presence of recurrence seizure within first 6 h					
	Presence seizure (n=31)	**Absence seizures (n=111)**	**p value**	**Unadjusted odds ratio 95% CI**	**Adjusted odds ratio 95% CI**
Gender n (%) Male Female	 14 (45.2) 17 (54.8)	 58 (52.3) 53 (47.7)	 0.4	 0.75 (0.33 to 1.6)	 -
Age median (IQR 25-75%)	35 (20 to 43)	31 (24 to 43)	0.59	0.9 (0.96 to 1.025)	-
Comorbidities n (%) Chronic hypertension Coronary artery diseases Diabetes mellitus Cerebral palsy Cerebra-vascular event Psychiatric disorders Chronic alcohol use Others	 1 (3.2) 0 (0) 1 (3.2) 4 (12.9) 2 (6.5) 3 (9.7) 4 (12.9) 7 (22.6)	 9 (8.1) 6 (5.4) 5 (4.5) 1 (0.9) 6 (5.4) 13 (11.7) 7 (6.3) 16 (14.4)	 0.6 0.3 1 **0.008** 1 1 0.2 0.2	 0.3 (0.04 to 3.1) N/A 0.7 (0.79 to 6.2) 16.2 (1.7 to 151) 1.2 (0.2 to 6.2) 0.8 (0.2 to 3.1) 2.2 (0.6 to 8.01) 1.7 (0.6 to 4.6)	 - - - N/A[a] - - - -
The history of epilepsy n (%) Epilepsy history in family Previously meningitis history Febrile convulsion history Difficult birth history Severe head trauma history* Previously status epilepticus history Hospital admission history due to epilepsy ICU admission history due to epilepsy Intubation history due to epilepsy Epileptic surgery history Cluster-type epilepsy history**	 4 (12.9) 2 (6.5) 6 (19.4) 6 (19.4) 8 (25.8) 6 (19.4) 11 (35.5) 5 (16.1) 1 (3.2) 0 20 (64.5)	 24 (21.6) 4 (3.6) 35 (31.5) 19 (17.1) 27 (24.3) 15 (13.5) 37 (33.3) 12 (10.8) 2 (1.8) 1 (0.9) 55 (49.5)	 0.2 0.6 0.1 0.7 0.8 0.4 0.8 0.5 0.5 1 0.1	 0.5 (0.1 to 1.6) 1.8 (0.3 to 10.5) 0.5 (0.1 to 1.3) 1.1 (0.4 to 3.2) 1.08 (0.4 to 2.6) 1.5 (0.5 to 4.3) 1.1 (0.4 to 2.5) 1.5 (0.5 to 4.9) 1.8 (0.1 to 20) N/A 1.8 (0.8 to 4.2)	 - - - - - - - - - N/A[a] -
Drug history n (%) AED use Nonadherent to AED therapy Unused last of AED dosage Polytherapy AED use Third-generation AED using	 30 (96.8) 15 (48.4) 15 (48.4) 11 (35) 21 (67.7)	 102 (91.9) 33 (29.7) 55 (49.5) 36 (32) 70 (63.1)	 0.3 0.052 0.9 0.7 0.6	 2.6 (0.3 to 22) 2.2 (0.9 to 4.9) 1.04 (0.4 to 2.3) 1.1 (0.4 to 2.6) 1.2 (0.5 to 2.8)	 - **2.5 (1.01 to 6.4)** - - -
Age of when diagnosed epilepsy median (IQR 25-75%)	14 (7-21)	19 (13.5-28.5)	0.3	0.98 (0.95 to 1.01)	-
Duration time since diagnosed epilepsy/year median (IQR 25-75%)	22 (1-38)	8 (2.75-16)	0.1	1.02 (0.9 to 1.05)	-
The presence of weekly routine seizures in history n (%)	9 (29)	13 (11.7)	**0.02**	**3.08 (1.1 to 8.1)**	2.7 (0.8 to 8.8)
The presence of monthly routine seizures in history n (%)	11 (35.5)	44 (39.6)	0.6	0.8 (0.3 to 1.9)	-
Epilepsy etiology n (%) Symptomatic[#] Idiopathic[##]	 20 (64.5) 11 (35.5)	 73 (65.8) 38 (34.2)	 0.8	 1.07 (0.4 to 2.4)	 -
The state of consciousness on admission to ED n (%) Active seizure/postictal period Conscious	 21 (67.8) 10 (32.2)	 33 (29.7) 78 (70.3)	 **<0.001**	 **4.9 (2.1 to 11.6)**	 **4.3 (1.7 to 11)**
Duration of postictal period (minute) median (IQR 25-75%)	30 (20-60)	20 (10-40)	**0.03**	**1.012 (1.002 to 1.02)**	1.007 (0.99 to 1.01)
Seizure features n (%) Presence aura in the pre-seizure period Prolonged postictal period*** Seizure period 06:00-12:00 12:00-20:00 20:00-06:00 Relationship of seizure to sleep On sleeping Awake	 9 (29) 10 (32.3) 7 (22.6) 9 (29) 15 (48.4) 9 (29) 22 (19.8)	 37 (33.3) 25 (22.5) 48 (43.2) 30 (27) 33 (29.7) 22 (71) 89 (80.2)	 0.6 0.2 0.07 0.2	 0.8 (0.3 to 1.9) 1.6 (0.6 to 3.9) N/A 0.6 (0.2 to 1.4)	 - - - -

Table 2. Continued

	Presence seizure (n=31)	Absence seizures (n=111)	p value	Unadjusted odds ratio 95% CI	Adjusted odds ratio 95% CI
Clinical features n (%)					
Fever higher than 38 °C in last 24 h	8 (25.8)	15 (13.5)	0.1	2.2 (0.8 to 5.8)	-
Disturbed sleep in the last 48 h	21 (67.7)	58 (52.3)	0.1	1.9 (0.8 to 4.4)	-
Alcohol intake in the last 24 h	0 (0)	5 (4.5)	N/A	N/A	N/A[a]
Acute traumatic injury	12 (38.7)	45 (40.5)	0.8	0.9 (0.4 to 2.0)	-
Psychotropic drug use in the last 24 h	4 (12.9)	3 (2.7)	**0.04**	**5.3 (1.12 to 25.2)**	N/A[a]
Acute psychological stress in the last week	18 (58.1)	69 (62.2)	0.6	0.8 (0.3 to 1.8)	-
Changing AED dosage	7 (22.6)	14 (12.)	0.2	2.02 (0.7 to 5.5)	-
Use of herbal medicine	0 (0)	4 (3.6)	N/A	N/A	N/A[a]
Cerebral localization of epilepsy**** n (%)					
Frontal	2 (6.5)	7 (6.3)			
Temporal	6 (19.4)	16 (14.4)			
Parietal	9 (29)	40 (36)	0.8	N/A	-
Occipital	3 (9.7)	9 (8.1)			
Limbic	0 (0)	5 (4.5)			
Unknown	11 (35.5)	34 (30.6)			
Vital signs on admission median (IQR 25-75%)					
Systolic blood pressure: mmHg	120 (109 to 140)	120 (110-132)	0.9	0.99 (0.97 to 1.02)	-
Diastolic blood pressure: mmHg	70 (65 to 80)	70 (65-80)	0.9	1.02 (0.9 to 1.04)	-
Pulse - beat/min	100 (82 to 116)	90 (79-100)	**0.009**	**1.039 (1.012 to 1.066)**	1.027 (0.99 to 1.05)
Fever - °C	36.4 (36 to 37.8)	36.3 (36.1 to 36.7)	0.1	2.06 (0.8 to 3.5)	-
Blood sugar: mg/dL	109 (96 to 131)	104 (91 to 120)	0.1	1.02 (0.9 to 1.02)	-
Oxygen saturation - %	95 (92 to 97)	96 (94 to 98)	0.3	0.9 (0.7 to 1.07)	-
Glasgow-coma scale	11 (9 to 15)	15 (13 to 15)	**<0.001**	0.7 (0.6 to 0.9)	-
Laboratory findings median (IQR 25-75%)					
pH	7.30 (7.20-7.40)	7.39 (7.34-7.42)	**<0.001**	**0.002 (0.001 to 0.08)**	Not included[b]
PCO_2 - mmHg	41 (35-47)	40 (35-46)	0.5	1.03 (0.9 to 1.08)	-
Bicarbonate - mmol/L	22 (16-26)	23 (20-26)	0.3	0.9 (0.8 to 1.03)	-
Lactate - mEq/L	6.2 (3.2-9.2)	2.8 (1.8-4.8)	**<0.001**	**1.2 (1.08 to 1.3)**	1.09 (0.96 to 1.2)
White blood cell - $x10^3/\mu L$	12.7 (8.8-15.2)	7.9 (6.7-10.1)	**<0.001**	**1.2 (1.1 to 1.3)**	**1.2 (1.08 to 1.3)**
Neutrophil - $x10^3/\mu L$	8.9 (4.6-11.7)	4.7 (3.9-6.6)	**<0.001**	**1.2 (1.1 to 1.3)**	Not included[c]
Lymphocyte - $x10^3/\mu L$	2.4 (1.2-4.5)	2.3 (1.69-3.2)	0.8	1.01 (0.9 to 1.1)	-
Hemoglobin - g/dL	14 (12.8-15.5)	14.1 (12.8-15.5)	0.8	1.01 (0.8 to 1.2)	-
Platelet - $x10^3/\mu L$	223 (182-299)	240 (191-287)	0.8	0.99 (0.97 to 1.003)	-
Creatinine	0.8 (0.7-1)	0.8 (0.7-0.9)	0.7	1.12 (0.1 to 6.8)	-
ALT - IU/L	16 (10-25)	14 (11-21)	0.6	0.99 (0.97 to 1.01)	-
Total bilirubin: mg/dL	0.3 (0.2-0.36)	0.3 (0.15-0.4)	0.7	0.4 (0.1 to 2)	-
Sodium - mEq/L	138 (137-140)	138 (137-140)	0.9	1.01 (0.9 to 1.1)	-
Potassium - mEq/L	3.9 (3.7-4.1)	4.1 (3.8-4.3)	0.06	0.3 (0.1 to 1.02)	-
Calcium - mg/dL	9.5 (9-10)	9.6 (9.2-9.9)	0.06	0.8 (0.4 to 1.5)	-
Length of stay ED median (IQR 25-75%)	8 (6-12)	4 (4-6)	0.1		-
IV AED needing in ED n (%)	23 (74.2)	4 (3.6)	**<0.001**		Not included[d]

*Severe head trauma history: Presence of head trauma requiring hospitalization or surgical intervention and accompanying altered mental status in history.
**Cluster-type seizure: Two or more seizures in 24 h.
***Prolonged postictal period: Prolonged postictal period compared to the previous postictal period based on the anamnesis taken from relatives.
****Location detected on EEG that performed after the last seizure attack.
#Epilepsy disease secondary to organic lesion (intracranial hemorrhage, ischemic stroke, etc.).
##Epilepsy that starts unrelated to any organic lesion.
[a]: Insufficient sample size in cells to perform regression analysis.
[b]: pH variable was found to be highly correlated with lactate values. Therefore, it was excluded in the regression model.
[c]: Neutrophil variable was found to be highly correlated with white blood cell values. Therefore, it was excluded in the regression model.
[d]: It was considered as an alternative outcome.
AED: Anti-epileptic drug, ED: Emergency department, N/A: Not applicable

Table 3. Demographical and clinical characteristics of patients according to the presence of recurrence seizure within first 24 h					
	Presence seizures (n=39)	**Absence seizures (n=103)**	**p value**	**Unadjusted odds ratio 95% CI**	**Adjusted odds ratio 95% CI**
Gender n (%)					
Male	17 (43.6)	55 (53.4)	0.2	0.64 (0.3 to 1.4)	-
Female	22 (56.4)	48 (46.6)			
Age median (IQR 25-75%)	34 (22 to 41)	31 (25 to 44)	0.4	0.99 (0.96 to 1.019)	-
Comorbidities n (%)					
Chronic hypertension	1 (2.6)	9 (8.7)	0.2	0.27 (0.03 to 2.4)	-
Coronary artery diseases	0 (0)	6 (5.8)	N/A	N/A	-
Diabetes mellitus	1 (2.6)	5 (4.9)	1	0.5 (0.05 to 4.5)	-
Cerebral palsy	4 (10.3)	1 (1)	**0.02**	**11 (1.2 to 107)**	N/A[a]
Cerebra-vascular event	2 (5.1)	6 (5.8)	1	0.8 (0.1 to 4.5)	-
Psychiatric disorders	5 (12.8)	11 (10.7)	0.7	1.2 (0.3 to 3.8)	-
Chronic alcohol use	9 (23.1)	14 (13.6)	0.1	1.5 (0.4 to 5.6)	-
Others	4 (10.3)	7 (6.8)	0.4	1.9 (0.7 to 4.8)	-
The history of epilepsy n (%)					
Epilepsy history in family	6 (15.4)	22 (21.4)	0.4	0.6 (0.2 to 1.8)	-
Previously meningitis history	2 (5.1)	4 (3.9)	0.6	1.3 (0.2 to 7.6)	-
Febrile convulsion history	11 (28.2)	30 (29.1)	0.9	0.9 (0.4 to 2.1)	-
Difficult birth history	7 (17.9)	18 (17.5)	0.9	1.03 (0.39 to 2.7)	-
Severe head trauma history*	11 (28.2)	24 (23.3)	0.5	1.2 (0.5 to 2.9)	-
Previously status epilepticus history	7 (17.9)	14 (13.6)	0.5	1.3 (0.5 to 3.7)	-
Hospital admission history due to epilepsy	16 (41)	32 (31.1)	0.2	1.5 (0.7 to 3.3)	-
ICU admission history due to epilepsy	6 (15.4)	11(10.7)	0.5	1.5 (0.5 to 4.4)	-
Intubation history due to epilepsy	1 (2.6)	2 (1.9)	1	1.3 (0.1 to 15)	-
Epileptic surgery history	0	1 (1)	-	N/A	N/A[a]
Cluster-type epilepsy history**	28 (71.8)	47 (45.6)	**0.005**	**3.03 (1.3 to 6.7)**	2.1 (0.8 to 5.8)
Drug history n (%)					
AED using	38 (97.4)	94 (91.3)	0.2	3.6 (0.4 to 29)	-
Nonadherent to AED therapy	18 (46.2)	30 (29.1)	0.056	2.08 (0.9 to 4.4)	**2.5 (1.09 to 6.5)**
Unused last of AED dosage	19 (48.7)	51 (49.5)	0.9	1.03 (0.4 to 2.1)	-
Polytherapy AE use	16 (41)	30 (29.1)	0.07	1.8 (0.8 to 4.03)	**2.9 (1.08 to 8.1)**
Third-generation AED using	28 (71.8)	63 (61.2)	0.2	1.6 (0.7 to 3.6)	-
Age of when diagnosed epilepsy median (IQR 25-75%)	17 (12 to 26)	22 (12 to 30)	0.1	0.98 (0.95 to 1.04)	-
Duration time since diagnosed epilepsy/year median (IQR 25-75%)	13 (4 to 23)	8 (2 to 18)	0.1	1.02 (0.9 to 1.05)	-
The presence of weekly routine seizures in history n (%)	11 (28.2)	11 (10.7)	**0.01**	**3.2 (1.2 to 8.3)**	**3.9 (1.2 to 12)**
The presence of monthly routine seizures in history n (%)	14 (35.9)	41 (39.8)	0.6	0.8 (0.3 to 1.8)	-
Epilepsy etiology n (%)					
Symptomatic[#]	26 (66.7)	67 (65)	0.8	0.9 (0.4 to 2.02)	-
Idiopathic[##]	13 (33.3)	36 (35)			
The state of consciousness on admission to ED n (%)					
Active seizure/postictal period	23 (59)	31 (30.1)	**0.002**	**3.3 (1.5 to 7.1)**	1.5 (0.5 to 4.5)
Conscious	16 (41)	72 (69.9)			
Duration of postictal period (minute) median (IQR 25-75%)	30 (20-60)	20 (10-30)	**0.009**	**1.014 (1.003 to 1.025)**	**1.01 (1.001 to 1.026)**
Seizure features n (%)					
Presence aura in the pre-seizure period	13 (33.3)	33 (32)	0.8	1.06 (0.4 to 2.3)	-
Prolonged postictal period***	13 (33.3)	22 (21.4)	0.1	1.8 (0.8 to 4)	-
Seizure period					
06:00-12:00	11 (28.2)	44 (42.7)			
12:00-20:00	10 (25.6)	29 (28.2)	0.1	N/A	-
20:00-06:00	18 (46.2)	30 (29.1)			
Relationship of seizure to sleep					
On sleeping	11 (28.2)	20 (19.4)	0.2	0.6 (0.2 to 1.4)	-
Awake	28 (71.8)	83 (80.6)			

Table 3. Continued

	Presence seizures (n=39)	Absence seizures (n=103)	p value	Unadjusted odds ratio 95% CI	Adjusted odds ratio 95% CI
Clinical features n (%)					
Fever higher than 38 °C in last 24 h	8 (20.5)	15 (14.6)	0.3	1.5 (0.5 to 3.9)	-
Disturbed sleep in the last 48 h	24 (61.5)	55 (53.4)	0.3	1.3 (0.6 to 2.9)	-
Alcohol intake in the last 24 h	0 (0)	5 (4.9)	-	N/A	N/A[a]
Acute traumatic injury	14 (35.9)	43 (41.7)	0.5	0.7 (0.3 to 1.6)	-
Psychotropic drug use in the last 24 h	5 (12.8)	2 (1.9)	**0.01**	**7.4 (1.3 to 25.2)**	N/A[a]
Acute psychological stress in the last week	24 (61.5)	63 (61.2)	0.9	1.01 (0.4 to 2.1)	-
Changing AED dosage	7 (17.9)	14 (13.6)	0.5	1.3 (0.5 to 3.7)	-
Use of herbal medicine	0 (0)	4 (3.9)	N/A	N/A	N/A[a]
Cerebral localization of epilepsy**** n (%)					
Frontal	2 (5.1)	7 (6.8)			
Temporal	7 (17.9)	15 (14.6)			
Parietal	14 (35.9)	35 (34)	0.2	N/A	-
Occipital	3 (7.7)	9 (8.7)			
Limbic	0 (0)	5 (4.9)			
Unknown	13 (34)	32 (31.1)			
Vital signs on admission Median (IQR 25-75%)					
Systolic blood pressure: mmHg	120 (110 to 140)	120 (110 to 132)	0.8	0.99 (0.97 to 1.02)	-
Diastolic blood pressure: mmHg	70 (64 to 75)	70 (65 to 80)	0.4	1.02 (0.9 to 1.04)	-
Pulse - beat/min	95 (82 to 110)	90 (78 to 100)	**0.02**	**1.039 (1.012 to 1.066)**	1.009 (0.9 to 1.04)
Fever - C°	36.4 (36.1 to 37)	36.4 (36 to 36.7)	0.3	2.06 (0.8 to 3.5)	-
Blood sugar: mg/dL	105 (92 to 122)	105 (91 to 120)	0.5	1.02 (0.9 to 1.02)	-
Oxygen saturation - %	95 (93 to 97)	96 (94 to 98)	0.1	0.9 (0.7 to 1.07)	-
Glasgow-coma scale	13 (10 to 15)	15 (13 to 15)	**0.003**	0.83 (0.72 to 0.95)	Not included[b]
Laboratory findings median (IQR 25-75%)					
pH	7.35 (7.25-7.4)	7.39 (7.34-7.42)	**<0.006**	**0.001 (0.0001 to 0.2)**	Not included[c]
PCO_2 - mmHg	41 (36-48)	40 (35-45)	0.4	1.03 (0.9 to 1.08)	-
Bicarbonate - mmol/L	24 (17-26)	23 (23-26)	0.6	0.97 (0.91 to 1.03)	-
Lactate - mEq/L	5.4 (2.8-8.5)	2.7 (1.8-5.2)	**<0.001**	**1.15 (1.04 to 1.2)**	1.12 (0.99 to 1.2)
White blood cell - $x10^3/\mu L$	11.6 (7.7-14.4)	7.9 (6.6-10.1)	**<0.001**	**1.2 (1.1 to 1.3)**	**1.18 (1.06 to 1.3)**
Neutrophil - $x10^3/\mu L$	7.2 (4.5-10.8)	4.7 (3.8-6.5)	**<0.001**	**1.2 (1.1 to 1.38)**	Not included[d]
Lymphocyte - $x10^3/\mu L$	2.4 (1.3-4.1)	2.3 (1.7-3.1)	0.8	0.99 (0.8 to 1.1)	-
Hemoglobin - g/dL	14.1 (13-15.5)	14 (12.7-15.5)	0.5	1.06 (0.8 to 1.2)	-
Platelet - $x10^3/\mu L$	241 (182-296)	234 (187-290)	0.9	0.99 (0.98 to 1.003)	-
Creatinine	0.8 (0.7-0.9)	0.8 (0.7-0.9)	0.8	0.6 (0.1 to 3.6)	-
ALT - IU/L	14 (10-23)	14 (11-21)	0.9	0.99 (0.97 to 1.01)	-
Total Bilirubin: mg/dL	0.3 (0.2-0.3)	0.3 (0.1-0.4)	0.4	0.3 (0.08 to 1.4)	-
Sodium - mEq/L	138 (137-141)	138 (137-140)	0.8	1.03 (0.9 to 1.1)	-
Potassium - mEq/L	4 (3.8-4.1)	4.1 (3.8-4.3)	0.1	0.4 (0.1 to 1.1)	-
Calcium - mg/dL	9.7 (9-9.9)	9.5 (9.2-9.8)	0.4	0.99 (0.93 to 1.05)	-
The length of stay ED median (IQR 25-75%)	6 (5 to 12)	4 (4 to 6)	**<0.001**	**1.6 (1.3 to 2.02)**	Not included[e]
IV AED needing in ED n (%)	23 (59)	4 (3.9)	**<0.001**	**35 (10 to 116)**	Not included[e]

*Severe head trauma history: Presence of head trauma requiring hospitalization or surgical intervention and accompanying altered mental status in history.
**Cluster-type seizure: two or more seizures in 24 h.
***Prolonged postictal period: Prolonged postictal period compared to the previous postictal period based on the anamnesis taken from relatives.
****Location detected on EEG that performed after the last seizure attack.
#Epilepsy disease secondary to organic lesion (Intracranial hemorrhage, ischemic stroke, etc.).
##Epilepsy that starts unrelated to any organic lesion.
[a]: Insufficient sample size in cells to perform regression analysis.
[b]: Glasgow coma scale was found to be highly correlated with "State of Consciousness on admission to ED" variable. Therefore, it was excluded in the regression model.
[c]: pH variable was found to be highly correlated with lactate values. Therefore, it was excluded in the regression model.
[d]: Neutrophil variable was found to be highly correlated with white blood cell values. Therefore, it was excluded in the regression model.
[e]: It was considered as an alternative outcome.
AE: Antiepileptic, ED: Emergency department, N/A: Not applicable

11.02). Similarly, in a retrospective study by Chen et al. (17) on epilepsy patients older than 16 years, symptomatic generalized epilepsy, a history of status epilepticus, and AED treatment failure (two or more AEDs' failure) were risk factors for the occurrence of SC. In the same study, Chen et al. (17) reported that patients who experienced SC were significantly less likely to be seizure-free for 1 year (27.8%) compared with patients who did not experience SC (50.9%). The main difference between these studies and our study is that they focused on SC that can be experienced in any period, whereas our study focused on ARSs within the early period after the last seizure attack. The studies by Detyniecki et al. (14) and Chen et al. (17) appear to point to two primary risk factors for SC or ARS: a history of SC in the previous year and AED treatment failure. In our study, although a history of cluster-type epilepsy was not a significant predictor for ARS in the multivariate analysis, the ratio of cluster-type epilepsy in the ARS group was higher than that in the non-ARS group (71.8% vs 45.6%) in the univariate analysis. We believe that the number of AEDs used during a lifetime, a risk factor for SC in the study by Detyniecki et al. (14), treatment failure with two or more AEDs, a risk factor for SC in the study by Chen et al. (17), and AED polytherapy, which was a risk factor for ARS in our study, may be related to AED resistance. We conclude that a history of AED resistance is a crucial risk factor for SC and ARS.

Similar to our study, Choquet et al. (18) conducted a prospective study aimed at determining the frequency and predictors of ARS in the early period (at least one ARS within the first 24 hr) after admission to the ED. This study included not only patients with a confirmed diagnosis of epilepsy but also patients with new-onset seizures. The frequency of ARS in their study was 18.4%, and the GCS of the patients was lower than 15 points on admission. Age (i.e., older than 40 y) and a history of alcoholism were risk factors for ARS within the first 24 h after admission with a seizure. In our study, although alcoholism and older age were not predictive factors, a low GCS score seemed to be an important predictor of ARS. However, we did not include a low GCS score as a variable in the regression model because of its high correlation with state of consciousness on admission to the ED. We reported the presence of active seizures/postictal period on admission as predictors instead of a low GCS score.

Finally, in a study on 94 epilepsy patients older than 14 years, Kılıc et al. (19) evaluated the diagnostic performance of venous blood gases for ARS within the follow-up period in the ED in patients who were admitted to the ED with seizures. The authors reported that lactate, pH, base excess, and bicarbonate values in venous blood gases measured within 1 h after the last epileptic seizure episode appeared to be helpful in predicting ARS in the early period with high accuracy. Similarly, in our study, lactate and pH values seemed to be potential predictors of ARS in the univariate analysis, although they were not significant predictors of the risk of ARS in the multivariate analysis. Unlike previous studies, WBC count was identified as a predictor factor for ARS in our study. It has been reported that increase in WBC count in seizures can be related to increasing muscle activity and prolonged muscle activity can cause more increasing WBC count by several studies (20,21). Therefore, we think that prolonged seizures (mean prolonged muscle activity and more increasing WBC count) can be related to recurrence seizures. We believe that prognostic values of WBC count for recurrence seizures is not sufficiently studied in the literature.

Study Limitations

This study has some limitations. First, we think that our sample size could be limited to determine most factors predicting the risk of ARS in the multivariate regression analysis. Second, although we tried to include as many demographic and clinical variables as possible in our model, some risk factors may have been overlooked. Finally, the definition of ARS in our study may be a limitation. There is no standard definition of SC or ARS, with the definitions for both varying in the literature. Therefore, it is not easy to generalize and compare our findings with those of previous studies, which may have employed different SC and ARS definitions.

Conclusion

Despite the limitations of the present study, it showed that after a first seizure, ARS is not rare in the early period after admission to the ED, with an incidence of 21.8% in the first 6 h and 27.4% in the first 24 h. In our study, nonadherent to AED therapy, active seizures/postictal period on admission, and white blood cell count seemed to be related to an increase in ARS within the first 6 h and that nonadherent to AED therapy, AED polytherapy, a history of weekly seizures, and the postictal period duration appeared to be associated with an increase in ARS within the first 24 h.

As a result, we think that physicians should be aware of the need to follow up patients with 24-h ARS risk factors in the EDs for a longer time or to inform their relatives about the risk of ARS in case of a decision to be discharged.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Keçiören Training and Research Hospital of Local Ethics Committee (protocol id and date: 48865165-020/07.10.2018).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ş.Ç., D.Y.C., Concept: H.Ş.Ç., Ş.K.Ç., D.Y.C., E.E., Y.Ç., Design: H.Ş.Ç., Ş.K.Ç., D.Y.C., E.E., Y.Ç., Data Collection or Processing: H.Ş.Ç., D.Y.C., Y.Ç., Analysis or Interpretation: Ş.K.Ç., E.E., Y.Ç., Literature Search: H.Ş.Ç., Ş.K.Ç., E.E., Writing: H.Ş.Ç., Ş.K.Ç., D.Y.C., E.E.

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

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

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