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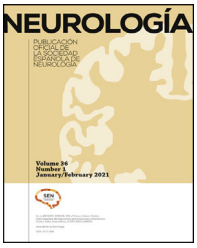

ORIGINAL ARTICLE

Status epilepticus management and mortality risk factors: a retrospective study☆

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KEYWORDS
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Abstract
Introduction: Status epilepticus (SE) is a neurological emergency with relatively high mortality rates. In this study, we analysed the management of SE and identified mortality risk factors that may be addressed with educational interventions or modifications to hospital protocols.
Methods: In this retrospective study, we analysed demographic, treatment, and outcome data from 65 patients (mean age, 59 years [range, 44.5-77]; 53.8% women) who were admitted to our tertiary hospital during an 18-month period and met the 2015 International League Against Epilepsy criteria for SE.
Results: Thirty patients (46.2%) had history of epilepsy. The most frequent causes of SE were cerebrovascular disease (27.7%) and systemic infection (16.9%). The following deviations were observed in the administration of the antiepileptic drugs: benzodiazepines were used as first option in only 33 (50.8%) patients; the combination of 2 benzodiazepines was recorded in 7 cases (10.8%); and lacosamide was used as an off-label drug in 5 patients (7.7%). Electroencephalography studies were performed in only 26 patients (40%); and only 5 studies (7.7% of patients) were performed within 12 hours of seizure onset. The mortality rate was 21.5%. Acute stroke and cerebrovascular complications were associated with higher mortality rates, while previous history of epilepsy and admission to intensive care were related to better prognosis ($P < .05$).

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Conclusions: To improve SE management and reduce mortality rates, training activities targeting emergency department physicians should be implemented, together with elective intensive care admission for patients with multiple mortality risk factors (eg, absence of history of epilepsy, acute stroke, or cardiovascular complications).

PALABRAS CLAVE
Epilepsia;
Estatus epiléptico;
Factores de riesgo;
Fármacos antiepilépticos;
Complicaciones agudas;
Mortalidad

Manejo y factores de riesgo de mortalidad del estatus epiléptico: estudio retrospectivo

Resumen
Introducción: El status epiléptico (SE) es una emergencia neurológica con altas tasas de mortalidad. En este estudio, analizamos el manejo del SE e identificamos factores de riesgo de mortalidad en los que realizar intervenciones de mejora o modificaciones en los protocolos de actuación hospitalarios.
Métodos: Retrospectivamente, se analizaron los datos demográficos, de tratamiento y pronóstico de 65 pacientes (59 [44.5-77] años, 53.8% mujeres) que ingresaron en un hospital terciario cumpliendo los criterios de SE de la ILAE 2015, durante un periodo de 18 meses.
Resultados: Treinta (46.2%) pacientes tenían antecedentes de epilepsia. Las causas más frecuentes de SE fueron enfermedad cerebrovascular (27.7%) e infección sistémica (16.9%). Se registraron desviaciones respecto al tratamiento habitual: la administración de las benzodiazepinas como primer fármaco sólo en 33 (50.8%) pacientes, la combinación de dos benzodiazepinas en siete (10.8%) pacientes, y el uso ''off-label'' de lacosamida en cinco (7.7%) pacientes. El electroencefalograma (EEG) fue realizado únicamente en 26 (40%) pacientes y sólo cinco EEG (7.7% de pacientes) en las primeras 12 horas. La tasa de mortalidad fue del 21.5%. Ictus agudo y complicaciones cerebrovasculares se asociaron con mortalidad, mientras que epilepsia previa e ingreso en la unidad de cuidados intensivos (UCI) fueron factores de buen pronóstico ($p < 0.05$).
Conclusiones: Para mejorar el manejo del SE y reducir la tasa de mortalidad, sería recomendable implementar actividades formativas dirigidas a los profesionales del departamento de Urgencias, así como el ingreso electivo en UCI para pacientes con factores de riesgo (primera crisis epiléptica, con ictus agudo o complicaciones cardiovasculares).

Introduction

Status epilepticus (SE) is a neurological emergency that occurs either due to failure of the mechanisms of seizure termination or due to the occurrence of successive seizures, resulting in excessively prolonged periods of epileptic seizures. As a consequence, SE can result in neuronal death and/or alterations to neural networks.[1]

Demographic data on SE vary according to the population studied: incidence ranges from 6.2 to 15.8 cases per 100 000 population[2—7]; the sex more frequently affected depends on the country studied.[3,4,6—8] Rates of mortality due to SE treated in hospital differ between European countries, ranging from 7.6% to 39%.[3,4,7,9]

Treatment of SE encompasses 3 phases, defined according to the drugs administered: the acute phase, in which treatment consists of intravenous benzodiazepines; the second phase, ''established SE,'' treated with intravenous antiepileptic drugs (AED) including phenytoin, fosphenytoin, valproic acid, and levetiracetam; and the third phase, in which SE is refractory and patients require anaesthesia.[10] It should be noted that the specific AEDs used depend on the local availability of drugs, regional treatment and management guidelines, and population characteristics.[2,5,10] For example, intravenous lorazepam is unavailable in some countries,[2,11] whereas relatively new AEDs such as lacosamide may be used for off-label indications in selected hospitals.[12—16] In order to conduct descriptive studies, it is necessary to gather updated information on the clinical management and treatment of SE in order to identify differences between populations, potential differences in management, and mortality risk factors. The ultimate aim is to use the information gathered to create (or enhance) specific protocols to improve the management and prognosis of patients with SE.

This study analyses the management of SE in a tertiary-level hospital, presenting data on the demographic characteristics of the patients treated, the causes of SE, the AEDs used, and potential irregularities in management with regard to the established protocols. We also report mortality rates and risk factors, with a view to the implementation of training activities or protocol modifications in order to improve the prognosis of SE.

Patients and methods

Patient selection and data gathering

This retrospective study was conducted at a tertiary-level hospital and includes patients admitted between January 2014 and June

2015 with a diagnosis of SE (ICD-10 classification G41). We included patients meeting the International League Against Epilepsy (ILAE) diagnostic criteria for SE: *1)* generalised (tonic-clonic) convulsive seizures lasting longer than 5 minutes; *2)* focal motor seizures without impaired consciousness lasting longer than 10 minutes; or *3)* nonconvulsive status with impaired consciousness (subtle/absence SE) lasting longer than 10-15 minutes with electroencephalographic (EEG) evidence of continuous epileptiform activity.[1]

Time of SE onset was based on witness accounts of ictal symptoms reported in the clinical history. The end of SE was defined as: *1)* termination of ictal symptoms or *2)* lack of electrical activity compatible with SE on a subsequent EEG recording, for patients with subtle/nonconvulsive SE or under pharmacological sedation. Patients were classified according to SE semiology and EEG findings.[1]

We conducted a comprehensive review of patient medical records to gather data on patient demographic characteristics, type of SE, aetiology of SE, diagnostic procedures, EEG findings, AEDs administered (and order in which they were administered, dosage, and adverse reactions), SE duration, comorbidities, and prognosis (classified as the need for intubation and/or admission to the intensive care unit [ICU], death, or recovery). For each patient, we recorded the total number of SE episodes and their order of appearance. Data on recurrent SE were analysed separately.

Aetiology of SE was classified as: *1)* structural damage to the central nervous system (CNS), including: cerebrovascular disease (acute/previous ischaemic/haemorrhagic stroke, hypoxic/anoxic brain injury), arteriovenous malformations, abscesses, primary or metastatic tumour; *2)* reduced seizure threshold: reduced/missed dose of regular AED, onset of seizure threshold—lowering drug, systemic infection, alcohol abstinence, alteration of hydroelectrolytic metabolism, sleep deprivation; or *3)* unknown origin.

Acute complications were classified into 4 subgroups: *1)* cardiovascular processes: atrial fibrillation or haemodynamic instability; *2)* alterations of hydroelectrolytic metabolism: hyponatraemia, hyperkalaemia, liver or kidney failure; *3)* respiratory processes: acute respiratory distress syndrome or respiratory insufficiency; and *4)* systemic infections: respiratory or urinary tract infection. To eliminate potential confounding variables, cardiovascular and respiratory processes related to hypoxic/anoxic injury in patients with generalised convulsive myoclonic SE were excluded from the analysis of SE complications.

This study was approved by our hospital's research ethics committee.

Management of status epilepticus and complementary studies

In accordance with our hospital's management protocol, episodes of SE were attended by the emergency department medical team (at the place of occurrence, in cases with onset in hospital, or in the resuscitation area, in cases with onset outside hospital), according to the national and international clinical guidelines.[10,17] AEDs were administered in accordance with the national guidelines, with administration of benzodiazepines in the initial phase (avoiding infusion of 2 or more different benzodiazepines), followed by intravenous levetiracetam, valproic acid, or phenytoin if SE did not resolve.[17] Intravenous anaesthetics were used in cases of refractory SE, after ICU staff had secured the patient's airway. The attending physicians requested the intervention of the on-call neurologist when they deemed it necessary. EEG was only available at the emergency department during working hours. Emergency CT scans were performed in all cases, except when: *1)* the patient had history of SE; *2)* neurological examination did not detect any alterations; or *3)* the patient presented no signs of traumatic brain injury (TBI).

Statistical analysis

Statistical analysis was performed using the SPSS statistics software (version 19.0; Chicago, Illinois, USA). For patients presenting more than one episode of SE, we only used data from the first episode in the analysis of SE characteristics and mortality in order to avoid potential confounding variables and overestimation of the effect. Data on recurrent SE were analysed separately. Normal distribution of the sample was assessed using the Kolmogorov-Smirnov test. Differences between groups were calculated with the chi-square test, Mann-Whitney U test, or Kruskal-Wallis test, as appropriate. *P*-values < .05 were considered statistically significant. The Bonferroni correction was applied to adjust for multiple comparisons.

Predictive factors of mortality were studied with multinomial/multiple and binary logistic regression models including sex, age, AEDs administered, SE aetiology, SE subtype, detection of lesions in neuroimaging studies, use of anaesthetics, ICU admission, SE duration, number and type of acute complications, and assessment by the on-call neurologist. The results are expressed as relative risk (RR) or odds ratio (OR) and 95% confidence intervals (CI).

Results

Demographic and clinical characteristics

The demographic characteristics of the study population are summarised in Table 1.

We included 65 patients, 30 of whom (46.2%) presented history of epilepsy, with a total of 93 episodes of SE: 50 (76.9%) presented a single episode during the study period, 11 (16%) presented 2 episodes, and 4 (6.2%) presented 3 or more. As mentioned above, we only included each patient's first episode of SE in the analysis to avoid potential confounding variables; the analysis therefore includes a total of 65 episodes.

Thirty-five patients (53.8%) were receiving regular AED treatment, of whom 30 (46.2% of the total sample) had been diagnosed with epilepsy. The most frequently used AED was levetiracetam, followed by valproic acid. Most patients were receiving one (54.3% of patients treated on an outpatient basis) or 2 AEDs (14.3% of the patients treated). Patients receiving 3 or more AEDs presented more episodes of SE than those receiving 2 or fewer of these drugs (RR: 2.13 vs 0.92; $P = .004$); a total of 17 episodes were recorded in the former group.

Five patients with no history of epilepsy were receiving AEDs on an outpatient basis: 2 (3.1%) were receiving levetiracetam for primary prevention following CNS surgery; one (1.5%) was receiving gabapentin to alleviate neuropathic pain; and 2 (3.1%) were receiving valproic acid to treat psychiatric conditions.

Types and causes of status epilepticus

The classification and causes of SE are summarised in Table 1. The most frequent type was generalised convulsive SE. In 2 cases (2.15%), SE presented focal motor onset, progressing to generalised convulsive SE; another episode (1.1%) presented generalised onset subsequently progressing to subtle SE.

The most frequent causes of SE were structural damage to the CNS (38.5% of patients) and reduced seizure threshold (29.2%). The 2 most common causes of structural damage were acute/subacute cerebrovascular events (18 patients, 27.7%) and primary tumours of the CNS (10 patients, 15.4%). The 2 most frequent causes of reduced seizure threshold were systemic infection (16.9%) and reduced/missed doses of regular AEDs (15.4%). Patients receiving fewer than 3 AEDs did not present higher prevalence of reduced/missed doses than those receiving 3 or more ($P = .8$).

Table 1 Demographic variables, status epilepticus characteristics, and clinical outcomes of the study population.

	Patients (n = 65)	History of epilepsy (n = 30)[c]	First seizure (n = 35)	*P*
Age, years; median (p25-p75)	59 (44.5-77)	58 (42.5-72)	61 (49-79)	.4
Women, n (%)	35 (53.8)	17 (54.8)	18 (51.4)	.6
Regular AED				
Levetiracetam; n (%)	24 (36.9)	22 (73.3)	2 (5.7)	<.001[a]
Valproic acid; n (%)	5 (7.7)	3 (10)	2 (5.7)	.5
CBZ/OXC/ESL; n (%)	5 (7.7)	5 (16.7)	—	—
Other AEDs; n (%)	12 (18.5)	11 (36.7)	1 (2.9)	—
No. of SE episodes				
1; n (%)	50 (76.9)	20 (66.7)	30 (85.7)	.07
2; n (%)	11 (16.9)	8 (26.7)	3 (8.6)	.05[a]
3 or more; n (%)	4 (6.2)	2 (6.7)	2 (5.7)	.8
SE aetiology[b]				
Acute processes				
Reduced seizure threshold[d]; n (%)	19 (29.2)	12 (40)	7 (20)	.2
Acute ischaemic/haemorrhagic stroke[e]; n (%)	8 (12.3)	—	8 (22.9)	.006[a]
Chronic processes				
Previous stroke; n (%)	10 (15.4)	3 (10)	7 (20)	.2
Progressive processes				
Abscesses, tumour, TBI; n (%)	17 (26.2)	5 (16.7)	12 (34.3)	.3
Multiple aetiologies (acute, chronic, progressive); n (%)	10 (15.4)	3 (10)	7 (20)	.2
Unknown; n (%)	12 (18.5)	6 (20)	6 (17.1)	.7
SE classification				
Generalised convulsive SE; n (%)	32 (49.2)	11 (36.7)	21 (60)	.08
Focal motor SE; n (%)	16 (24.6)	7 (22.6)	9 (25.7)	.8
Subtle/absence SE; n (%)	17 (26.2%)	12 (4)	5 (14.3)	.07
Estimated SE duration				
< 12 h; n (%)	20 (30.8)	7 (23.3)	13 (37.1)	.2
12-24 h; n (%)	12 (18.5)	5 (16.7)	7 (20)	.9
24-48 h; n (%)	11 (16.9)	6 (20)	5 (14.3)	.9
48-72 h; n (%)	19 (29.2)	12 (40)	7 (20)	.1
> 72 h; n (%)	3 (4.6)	—	3 (8.6)	.1
Acute complications[f]; n (%)	26 (40)	10 (33.3)	16 (45.6)	.3
Anaesthesia and ICU admission; n (%)	29 (44.6)	12 (40)	17 (48.6)	.5

Table 1 (*Continued*)

	Patients (n = 65)	History of epilepsy (n = 30)[c]	First seizure (n = 35)	*P*
Multiple acute complications; n (%)	4 (28.6)	—	4 (11.4)	.03[a]
Systemic infection[g]; n (%)	20 (30.8)	9 (30)	11 (31.4)	.9
Cardiovascular processes; n (%)	6 (9.2)	—	6 (17.1)	.01[a]
Respiratory processes; n (%)	3 (4.6)	—	3 (8.6)	.1
Alterations of hydroelectrolytic metabolism; n (%)	10 (15.4)	3 (10)	7 (20)	.3
Residual focal neurological deficits; n (%)	5 (7.7)	1 (3.3)	4 (11.4)	.2
Mortality; n (%)	14 (21.5)	2 (6.7)	12 (34.3)	.007[a]

AED: antiepileptic drugs; CBZ: carbamazepine; ESL: eslicarbazepine; ICU: intensive care unit; ILAE: International League Against Epilepsy; OXC: oxcarbazepine; SE: status epilepticus; TBI: traumatic brain injury.

Results are expressed as median (p25-p75) or n (percentage of SE episodes), as appropriate.

[a] Statistically significant results (patients with history of epilepsy vs those with first seizures).

[b] According to the ILAE classification.

[c] Of the patients with history of epilepsy, epilepsy aetiology was structural in 19 (63.3%), cryptogenic in 4 (13.3%), and idiopathic in 7 (23.3%).

[d] Reduced seizure threshold includes administration of drugs that lower the seizure threshold, systemic infection, alcohol abstinence, alterations of hydroelectrolytic metabolism, and sleep deprivation.

[e] Seven patients (10.8%) presented acute ischaemic stroke and one (1.5%) presented acute haemorrhagic stroke.

[f] Cardiovascular processes (atrial fibrillation or haemodynamic instability); alterations of hydroelectrolytic metabolism (hyponatraemia, hyperkalaemia, liver or kidney failure); respiratory processes (acute respiratory distress syndrome or respiratory insufficiency); systemic infections (respiratory or urinary tract infection). Patients with multiple acute complications are included in all the corresponding categories; for example, a patient with systemic infection, alterations of hydroelectrolytic metabolism, and respiratory alterations would be included in the categories corresponding to multiple acute complications, systemic infection, alterations of hydroelectrolytic metabolism, and respiratory processes.

[g] Six patients (9.2%) presented respiratory infections, secondary to influenza A virus infection in one case (1.5% of all patients).

Management of status epilepticus

Table 1 also summarises the management of SE (duration, complications) in our sample. The exact duration of SE was recorded in 50 cases (76.9%), with a median duration of 37.5 minutes (p25-p75, 11.25-112.5). The duration of the remaining episodes of SE was estimated according to the notes of the attending physician in patients' medical records. Only 5 patients presented SE with duration equal to or shorter than 10 minutes: 3 with generalised convulsive SE and 2 with subtle SE. Patients with SE duration $\leq$ 10 minutes did not present significant differences with respect to patients with SE lasting > 10 minutes in terms of age, history of epilepsy, type of SE, or cause of SE (*P*-values ranging from .3 to .7) but did present higher prevalence of self-limited SE (80% vs 6.7%; *P* = .015).

In 8 cases (12.3%), infusion of benzodiazepines or AEDs was not needed. In 2 cases (3.1%) we were unable to obtain information regarding the treatment administered. The results discussed below, regarding the drugs used and the order in which they were administered, include the remaining 55 cases, for which detailed information was recorded by the attending physician (Table 2). We identified deviations from the standard treatment in 30 cases (46.2%), including the use of 2 different benzodiazepines, the use of an AED (not benzodiazepines) in the acute phase of SE, and off-label use of lacosamide (while this is not included in national guidelines,[17] no adverse reactions were recorded). Benzodiazepines were used in the acute phase in 33 patients (60% of the patients for whom treatment information was available). While diazepam was more commonly used in the acute phase, clonazepam was associated with a higher percentage of cases of SE termination (10.5% vs 42.9%; *P* = .03). Benzodiazepines were used as the second option in 9 cases, and 2 different benzodiazepines were used in combination in 7 cases. The combination of 2 different benzodiazepines was not associated with SE termination in any case. After benzodiazepines, levetiracetam was the most frequently used AED as the second option. Levetiracetam was used as the first option in the acute phase in 13 cases (23.6%): in 2 cases, the attending physician reported that the objective of administering the drug was to avoid the risk of benzodiazepines worsening pre-existing severe respiratory insufficiency. Phenytoin was the most common drug used in patients whose SE resolved after administration of a third AED.

Ten patients (18.2%) required anaesthesia, in isolation or in combination with muscle relaxants; this treatment was always administered in the ICU. Two patients (3.6%) received phenobarbital infusion and 4 (7.3%) received propofol. The anaesthetics used were not recorded in 4 cases (7.3%).

Twenty-nine patients (44.6% of the total) required support from the ICU medical team to control SE through induction of anaesthesia (10 patients; 34.5% of all ICU interventions) or to maintain airway permeability (19 patients; 65.5% of ICU interventions). Assistance was requested from the on-call neurologist in 25 of these cases (86.2% of ICU admissions), always after anaesthesia had been induced.

Complementary tests

EEG was only performed in 26 patients (40%), with only 5 (19.2%) undergoing EEG in the first 12 hours after onset. EEG detected activity compatible with SE in 6 cases (2.1% of all studies), and none of the studies performed at 72 hours after symptom onset detected epileptiform activity.

Forty-two patients (64.6%) underwent head CT scans.

Comorbidities, mortality, and risk factors

The acute complications recorded are summarised in Table 1. Twenty-six patients (40%) presented acute complications, which occurred in isolation in 24.6% of cases and in combination in 1%. The most frequent acute complications were systemic infections (30.8%) and alterations of hydroelectrolytic metabolism (15.4%).

Fourteen patients (21.5%) died. The analysis of mortality risk factors is summarised in Table 3. Acute ischaemic/haemorrhagic cerebrovascular events (as an aetiology of SE), cardiovascular complications, and presence of multiple acute complications significantly increased the risk of death. Four patients (6.2%) whose treatment diverged from the standard treatment died; however, no significant differences in mortality rates were found between these patients and those who received the standard treatment (*P* = .2). History of epilepsy and ICU admission were associated with lower mortality rates (*P* = .01 and *P* = .02, respectively). ICU admission showed a trend towards better prognosis after controlling for age, history of epilepsy, SE aetiology, and complications as possible confounding factors (*P* = .065). Nonetheless, mortality was associated with cardiovascular (*P* = .001) and respiratory complications (*P* = .003) in patients requiring ICU admission.

No deaths were recorded among the 5 patients (7.7%) with SE duration equal to or shorter than 10 minutes, whereas 14 patients (21.5%) with SE lasting longer than 10 minutes died (*P* = .8). We observed a trend towards higher mortality among patients with SE duration longer than 72 hours, compared to those with SE lasting less than 72 hours (66.7% mortality; *P* = .09). Unexpectedly, we observed a low mortality rate (1.5%) among patients whose SE lasted between 24 and 72 hours. Compared with the remaining patients, those aged between 18 and 60 years more frequently presented primary CNS tumours as the aetiology of SE (25% vs 0%, *P* = .002) and more frequently presented generalised convulsive SE (56.3% vs 21.2%, *P* = .004). In contrast, acute ischaemic stroke as SE aetiology was more frequent among patients older than 60 years (28.1%, vs 12.1% in younger patients; *P* = .005).

Discussion

This retrospective study characterises the causes and management of SE at a tertiary-level hospital, identifying deviations from standard treatment of SE and patients at high risk of mortality. The distribution of patients by sex, age, history of epilepsy, and regular AED treatment is consistent with previous series.[3—7] Similarly, the most frequent causes of SE were the same as those observed in previous national studies[5,18—21]: structural damage to the CNS (mainly acute and chronic cerebrovascular damage) and presence of factors that lower the seizure threshold (systemic infection, reduced/missed doses of regular AEDs). A noteworthy finding of our study was that patients receiving 3 or more regular AEDs were at greater risk of recurrent SE. While the small size of this group probably prevented us from identifying statistically significant differences, previous studies have shown that the use of multiple drugs is not only an indicator of drug-resistant epilepsy,[22] but is also associated with poor treatment adherence.[23,24] Poor treatment adherence, in turn, is associated with occurrence of SE.[19—21] To reduce the incidence of SE, measures should be implemented to improve treatment adherence, for example through greater monitoring or simplification/rational reduction of regular medications.

First-line treatment with clonazepam and levetiracetam was associated with higher rates of SE termination. Clonazepam was also associated with a higher rate of SE termination than diazepam; this is consistent with the findings of a previous study,[25] and is probably explained by the more prolonged action of clonazepam.[25] We detected several variations from the standard treatment for SE, which is based on national guidelines and the ILAE recommendations.[26] For example, drugs other than benzodiazepines were administered as the first-line treatment in a high percentage of cases (40.1%), and a combination of 2 different benzodiazepines was used on 7 occasions. The reason for these deviations was rarely recorded. The low percentage of emergency EEGs

Table 2 Antiepileptic drugs used in the 55 episodes of status epilepticus for which data were available on the drugs used and the order in which they were administered (data exclude 8 self-limited episodes of status epilepticus and 2 episodes for which the order in which drugs were administered is not recorded).

	Diazepam	Clonazepam	Midazolam	Clobazam	Valproic acid	Phenytoin	Levetiracetam	Lacosamide
Total; n (%)	21 (38.2)	21 (38.2)	7 (12.7)	2 (3.6)	17 (30.9)	20 (36.4)	33 (60.0)	5 (9.1)
Used as first AED[a]; n (%)	19 (34.5)	12 (21.8)	2 (3.6)	—	4 (7.3)	1 (1.8)	13 (23.6)	—
SE termination; n (%)	2 (10.5)	5 (41.7)	1 (50)	—	—	1 (100)	5 (38.5)	—
Used as second AED; n (%)	1 (1.8)	4 (7.2)	3 (5.5)	1 (1.8)	8 (14.5)	8 (14.5)	15 (27.3)	5 (9.1)[b]
SE termination; n (%)	—	1 (25.0)	—	1 (100)	3 (37.5)	4 (50.0)	4 (26.7)	4 (80.0)
Used as third/fourth AED; n (%)	1 (1.8)	5 (9.1)	2 (3.6)	1 (1.8)	(CP) 5 (9.1)	11 (20.0)	5 (9.1)	—
SE termination; n (%)	—	3 (60.0)	—	1 (100)	2 (50)	5 (45.5)	4 (80.0)	—

AED: antiepileptic drug; CP: continuous perfusion; SE: status epilepticus.

Results are expressed as n (percentage of patients for whom AED-related information was available), with the exception of data for SE termination, which are expressed as n (percentage of SE episodes that terminated after administration of the AED in question).

[a] Four patients received phenobarbital (n = 2; 3.6%) or propofol (n = 2; 3.6%) as the first drug.

[b] Lacosamide was used off-label in 5 cases: one patient with generalised convulsive SE, 2 with focal motor SE, and 2 with subtle/absence/nonconvulsive SE with impaired awareness.

Table 3 Risk factors related to mortality (n = 65).

	Death (n = 14)	Recovery (n = 51)	*P*	OR (95% CI)
Age (years)	66 (46-79.3)	58 (44-75)	.9	
< 18; n (%)	1 (7.1)	—	—	—
18-60; n (%)	5 (35.7)	27 (52.9)	.3	—
60-80; n (%)	7 (50)	14 (27.5)	.1	—
> 80; n (%)	1 (7.1)	10 (19.6)	.3	—
Women; n (%)	8 (57.1)	27 (52.9)	.7	
SE classification				
Generalised convulsive SE; n (%)	10 (71.4)	22 (43.1)	.07	—
Focal motor SE; n (%)	1 (7.1)	15 (29.4)	.2	—
Subtle/absence SE; n (%)	3 (21.4)	14 (27.4)	.4	—
SE duration; n (%)				
< 12 h; n (%)	6 (42.9)	14 (27.5)	.3	—
12-24 h; n (%)	5 (35.7)	7 (13.7)	.07	—
24-48 h; n (%)	—	11 (21.6)	—	—
48-72 h; n (%)	1 (7.1)	18 (35.3)	.07	—
> 72 h; n (%)	2 (14.3)	1 (2)	.09	—
History of epilepsy; n (%)	2 (14.3)	28 (54.9)	.01[a]	0.1 (0.02-0.7)
SE aetiology[b]				
Acute processes; n (%)	9 (64.3)	21 (41.2)	.3	
Reduced seizure threshold[c]; n (%)	2 (14.3)	20 (39.2)	.09	—
Acute ischaemic/haemorrhagic stroke; n (%)	7 (50)	1 (2)	.001[a]	50 (5.3-469)
Chronic processes				
Previous stroke; n (%)	1 (7.1)	9 (17.6)	.3	—
Progressive processes;(%)				
Abscesses, tumour, TBI; n (%)	2 (14.3)	15 (29.4)	.2	—
Multiple aetiologies (acute, chronic, progressive); n (%)	1 (7.1)	8 (15.7)	.4	—

Table 3 (*Continued*)

	Death (n = 14)	Recovery (n = 51)	*P*	OR (95% CI)
Unknown; n (%)	3 (21.4)	9 (17.6)	.7	—
Acute complications[d]				
Anaesthesia and ICU admission; n (%)	2 (14.3)	17 (33.3)	.02[a]	0.08 (0.02-0.4)
Multiple acute complications; n (%)	4 (28.6)	1 (2)	.002[a]	5.8 (1.8-19)
Systemic infection; n (%)	7 (50)	13 (25.5)	.08	
Cardiovascular processes; n (%)	4 (28.6)	2 (3.9)	.014[a]	9.8 (1.5-61)
Respiratory processes; n (%)	3 (21.4)	—	—	—
Alterations of hydroelectrolytic metabolism; n (%)	4 (28.6)	6 (11.8)	.1	—
Consultation with on-call neurologist; n (%)	1 (7.1)	6 (11.8)	.6	—

95% CI: 95% confidence interval; ILAE: International League Against Epilepsy; OR: odds ratio; recovery: SE termination (with or without clinical sequelae); SE: status epilepticus; TBI: traumatic brain injury.

Results are expressed as n (percentage of patients who died or recovered, respectively).

[a] Statistically significant results.

[b] According to the ILAE classification.

[c] Reduced seizure threshold includes administration of drugs that lower the seizure threshold, systemic infection, alcohol abstinence, alterations of hydroelectrolytic metabolism, and sleep deprivation.

[d] Patients with multiple acute complications are included in all the corresponding categories; for example, a patient with systemic infection, alterations of hydroelectrolytic metabolism, and respiratory alterations would be included in the categories corresponding to multiple acute complications, systemic infection, alterations of hydroelectrolytic metabolism, and respiratory processes.

performed may be attributed not only to the limited availability of EEG at the emergency department (only available during working hours), but also to the low rate of requests for the study. In the light of these findings, we recommend continued professional training to update professionals' knowledge of SE management (with particular emphasis on AED treatment and the importance of EEG studies in acute situations[27,28]), as well as periodic SE management drills, with a view to improving interventions by healthcare professionals and, as a result, the treatment and prognosis of patients with SE.

Mortality rates and mean age were greater in our sample than those reported in other European series,[3,4,7] but are similar to those of other Spanish studies.[5,8] Mortality rates progressively increased in line with SE duration (from less than 10 minutes to more than 72 hours). The low mortality rates observed in patients with SE duration between 24 and 72 hours may be associated with the admission of these patients to the ICU. Acute ischaemic stroke as the aetiology of SE and occurrence of multiple complications or cardiovascular complications were identified as factors related to mortality due to SE; this is compatible with the findings of other researchers.[29—34] History of epilepsy and ICU admission were protective factors in our series. In the light of our results, and with a view to improving the prognosis of patients with SE in our population, elective ICU admission could be implemented for patients whose profiles are associated with high risk of death (patients without history of epilepsy, SE duration longer than 10 minutes, cerebrovascular damage as the cause of SE, and/or cardiovascular complications).

Our study does present some limitations. Firstly, the biases inherent to retrospective studies may have interfered in identifying cases (patients without a definitive diagnosis of status epilepticus may have been excluded from data collection). SE may also have been misclassified (eg, focal motor SE with secondary generalisation may have been classified as generalised convulsive SE, or subtle SE may have been classified as syncope of uncertain aetiology), preventing us from establishing clinical-aetiological relationships. It should be noted that SE was mainly classified according to clinical manifestations, and that clinical data were recorded in emergency situations by emergency department physicians not specialised in neurology or epilepsy. Furthermore, some data were incomplete (exact duration of SE in some cases, weight-adjusted doses of AEDs, measurement and monitoring of concentration of AEDs in the blood), preventing us from establishing the association between SE, the level of effectiveness of AEDs/combinations of AEDs, risk factors, and mortality. Finally, the presence of unrecorded or unknown factors (related to SE aetiology, risk factors, or mortality) may have affected our results. Considering these limitations, there is a need for prospective studies with larger samples.

Conclusions

In order to improve the management and prognosis of SE, periodic training activities targeting emergency department staff should be implemented in order to update their knowledge regarding the management of AEDs (especially newer drugs) and to raise awareness of the need to perform emergency EEG studies. We also recommend implementing elective ICU admission for patients presenting characteristics associated with higher mortality rates (patients without history of epilepsy, SE duration longer than 10 minutes, acute stroke as the aetiology of SE, and/or associated cardiovascular complications).

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Author contributions

M. Hidalgo de la Cruz: study conception and design; clinical assessment; data collection, analysis, and interpretation; preparation of the first draft and approval of the final version of the article.

J.A. Miranda Acuña, E. Luque Buzo, B. Chavarria Cano, and E. Esteban de Antonio: clinical assessment; data collection, preparation/review of the first draft and approval of the final version of the article.

J. Prieto Montalvo: neurophysiological evaluation; data collection; preparation/revision of the first draft and approval of the final version of the article.

M.L. Galiano Fragua: study conception and design; clinical assessment; data analysis and interpretation; preparation/revision of the first draft and approval of the final version of the article; study supervision.

A. Massot-Tarrús: data analysis and interpretation; review of the first draft and approval of the final version of the article.

Conflicts of interest

A. Massot-Tarrús has received lecture honoraria and consulting fees from Bial, Eisai, and UCB Pharma.

M.L. Galiano Fragua has received lecture honoraria from Eisai.

The remaining authors have no conflicts of interest to declare.

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