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Evaluation of the Status Epilepticus Severity Score (STESS) as a predictor of in-hospital mortality in patients with status epilepticus: a retrospective observational study

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Abstract

Status epilepticus (SE) is a medical emergency characterized by continuous or recurrent epileptic activity with high mortality. The Status Epilepticus Severity Score (STESS is a tool used to assess the prognosis of SE patients; however, However, its validity and appropriate cut-off points have not been established in Mexico. The objective of this study was to describe the clinical characteristics of patients with SE in our medical center, identify the variables associated with mortality, and evaluate the predictive capacity of the STESS scale for in-hospital mortality. Material and Methods: This was a retrospective cohort study that included sixty patients diagnosed with SE between 2000 and 2020. The STESS scale was applied to assess prognosis. Data on clinical characteristics and in-hospital mortality were collected. Cox regression analysis was conducted to determine the risk of mortality for each point on the scale, and the area under the ROC curve was calculated to determine its discriminatory capacity. Results: The majority of patients presented with generalized convulsive SE (51.7%), and the most common etiology was acute symptomatic SE (46.7%). The in-hospital mortality rate was 40%. The risk of mortality increased by 38% for each point on the STESS scale (B=0.38, HR=1.48, 95% CI: 1.13-1.94, p=0.005). The area under the ROC curve was 0.72, with an optimal cut-off point of ≥3 points for discriminating in-hospital mortality. Conclusions: The STESS scale showed a significant association with in-hospital mortality and can be used as a predictive tool for adverse outcomes in patients with SE.

Keywords: *Status epilepticus, mortality, Status Epilepticus Severity Score*.

Introduction

Status epilepticus (SE) is a neurological emergency that requires immediate evaluation and treatment to prevent significant morbidity and mortality,[1,2] It is defined as "a condition that results from the failure of mechanisms responsible for terminating epileptic seizures or initiating mechanisms that lead to abnormally prolonged seizures".[3,4]

As a medical emergency that manifests on a continuum, SE presents at its severity extremes as refractory status epilepticus (RSE), where epileptic activity persists for more than 60 to 90 minutes after initiating treatment with a benzodiazepine and a first-line antiepileptic drug, and super-refractory status epilepticus (SRSE), which persists after 24 hours of treatment with intravenous anesthetics or recurs upon discontinuation/reduction of this therapeutic modality.[5,6] SRSE is associated with high morbidity and mortality due to brain damage (neuronal cell necrosis, gliosis, reorganization) resulting from the initiation of the excitotoxicity cascade, which typically begins after a few hours of continuous seizure activity. The reported mortality of SE varies depending on the etiology, ranging from 10% to 54%.

The most frequent etiologies include acute conditions such as acute myocardial infarction, intoxication, malaria, and encephalitis; remote conditions such as post-traumatic, post-encephalitic, and post-infarction states; progressive conditions such as brain tumors or dementias; and unknown or cryptogenic causes. Mortality increases with the duration of SE, and the causes can be complications of both the SE itself and its treatment. Common causes include hypotension, cardiopulmonary arrest, heart failure, liver failure, allergic reactions, disseminated intravascular coagulation, coagulation disorders, infections, and rhabdomyolysis, among others.[7-12]

Epidemiological information on SE is limited, particularly in developing countries. The incidence ranges from 18 to 41 cases per 100,000 inhabitants in the United States, compared to a lower incidence in Europe of 10-16 cases per 100,000 inhabitants.[7] The estimated age-standardized incidence is 4.61 to 18.3 cases per 100,000.6,[7,13] In Mexico, epilepsy has a prevalence of 10.8-20 cases per 1,000 inhabitants, representing 1.08-2% of the total population. However, data on the incidence of SE in Mexico are not available.[14]

The Status Epilepticus Severity Score (STESS) scale13 allows for the identification of patients with a favorable prognosis using a cut-off point of ≥3.[15] However, it has limited ability to identify patients with a poor prognosis and lacks universal adaptation.[16] The scale evaluates four clinical characteristics: **1**) level of consciousness, which can be alert or drowsy/confused and stupor or coma; **2**) predominant seizure type, including simple partial, complex partial, absence, myoclonic, generalized convulsive, or non-convulsive in a comatose state; **3**) patient age, divided into ≤65 years and >65 years; and **4**) presence or absence of a history of epilepsy. The scale was designed to predict in-hospital mortality in individuals diagnosed with status epilepticus.

The second scale, Epidemiology-based Mortality score in Status Epilepticus (EMSE), consists of 45 variables, and its original retrospective validation study reported that a cut-off point of ≥64 points had a 100% negative predictive value (NPV), 69% positive predictive value (PPV), and an accuracy of 89%. Kang et al.[17] conducted a comparative study between the EMSE scale and its variants, EMSE-EAC and EMSE-EACE, and the STESS score, finding no significant difference between these scales.[17] Furthermore, in 2016, Auklan et al.[18] reported that the STESS scale is an easily accessible and user-friendly tool for estimating in-hospital mortality, as most of the score components are associated with mortality following SE.

Objectives

The objective of this study was to describe the clinical characteristics of patients with status epilepticus in a Mexican tertiary care hospital, determine the variables associated with in-hospital mortality in this population, and assess the discriminatory capacity of the STESS scale as a predictor of in-hospital mortality, in order to validate this scale in the study population.

Materials and methods

A retrospective observational study was conducted on patients diagnosed with status epilepticus upon admission or during their hospital stay, who met the definition provided by the Neurocritical Care Society guidelines of 2012, and who were admitted to the Salvador Zubirán National Institute of Medical Sciences and Nutrition (INCMNSZ, for its acronym in Spanish) for medical care between January 2001 and December 2020. The inclusion criteria were as follows: adult patients aged ≥18 years with institutional records who were diagnosed with status epilepticus upon admission to the emergency department or during their hospital stay in any area of the hospital (emergency department, general wards, intermediate care, or intensive care unit). Patients with incomplete medical records or missing data necessary for calculating the STESS scale were excluded. All data were retrospectively obtained by reviewing electronic medical records. Patients were diagnosed with status epilepticus based on clinical assessment by the attending physician during their emergency department admission or hospital stay, and in some patients, the diagnosis was confirmed by an electroencephalogram. Follow-up was conducted through the electronic medical records until the date of hospital discharge. The type of status epilepticus was classified according to the International League Against Epilepsy (ILAE) 2017 classification, which defines it as a condition characterized by the presence of clinical and/or electroencephalographic epileptic activity lasting ≥5 minutes, or as the presence of recurrent epileptic activity without recovery of consciousness (return to the patient's baseline state) between seizures. Non-convulsive status epilepticus is defined as a condition characterized by non-convulsive clinical and/or electroencephalographic activity resulting in non-convulsive clinical manifestations. Subtypes of status epilepticus from these two general groups were included, as per the current ILAE classification. Based on etiology, status epilepticus was classified as acute symptomatic if it occurred within the first week of an acute neurological insult, remote symptomatic if it resulted from chronic cerebrovascular disease or sequelae of head trauma, and progressive symptomatic if it was related to a structural cause or mass effect.

Structural causes included primary central nervous system neoplasms, metastatic tumors, cerebral malformations, cerebral arteriovenous malformations, cavernous malformation, and lesions caused by multiple sclerosis.

The prognostic STESS scale was applied to evaluate its discriminatory capacity between patients with a poor prognosis (non-survivors) and those with a favorable prognosis (survivors). Since the scale is not routinely used in the emergency department, it was calculated retrospectively by extracting data from the medical records. Once the diagnostic criteria for status epilepticus were met, the following patient characteristics were extracted: level of consciousness, predominant seizure type, age, and history of epilepsy. The primary outcome (in-hospital mortality) was obtained through a review of the medical records by the principal investigator, noting the total number of patients who died and the date of death for each patient. This study was approved by the ethics and research committee of the Salvador Zubirán National Institute of Medical Sciences and Nutrition, with approval number URG-3928-/1-/0-1.

Statistical Analysis

Descriptive data are presented as median with interquartile range for quantitative variables and as frequency and percentage for qualitative variables. Comparisons of STESS scores at admission between survivors and non-survivors were performed using the Mann-Whitney U test. Cox regression models were used to determine the risk of mortality associated with different clinical variables and the STESS score. Variables were included using the Enter method. A p-value <0.05 was considered statistically significant. The analyses were conducted using SPSS software v.21, and figures were created using GraphPad Prism software v.9.0.1.

Results

A total of 75 patients with a diagnosis of status epilepticus were identified in the medical records during the specified period. Among them, 60 patients met the Neurocritical Care Society 2012 guidelines for inclusion in the study. Seven patients were excluded due to incomplete medical records that prevented the calculation of the STESS scale. Additionally, four patients did not meet the diagnostic criteria for status epilepticus, three patients had post-cardiopulmonary arrest status epilepticus, and one patient's medical record could not be located (Figure 1). Of the selected patients, 46 were female (76.7%), and the median age for both sexes was 49 years. Generalized convulsive status epilepticus was the most frequent type among the studied population, accounting for 51.7% (n=31) of cases, followed by generalized myoclonic status epilepticus, which accounted for 15% (n=9) of cases. It is worth noting that 85% of cases were refractory to treatment, with 26.7% of those classified as super-refractory. The overall mortality rate was high at 40% (n=24). The median length of hospital stay was 12 days (IQR: 7-23.5).

Table 1 summarizes the evaluated clinical characteristics. Acute symptomatic classification (status epilepticus caused by a known disease) was the most prevalent etiology (n=28, 46.7%). The main cause within this classification was multifactorial, including six patients with hypoxemia and sepsis, four patients with hypoxemia, hypercapnia, and shock, and two post-transplant patients who presented with drug toxicity. In 23% (n=14) of cases, a specific cause could not be established. Status epilepticus could only be classified in 56 patients due to insufficient information in the medical records to classify the remaining four episodes. A history of epilepsy was positive in 17 patients (28%).

Regarding reported comorbidities, 97% of patients had at least one comorbidity. The most associated pathology was systemic arterial hypertension, present in 20% of cases, followed by systemic lupus erythematosus (19%) and type 2 diabetes mellitus (15%) (Table 1).

Based on specific etiology (Table 2), within the acute symptomatic causes, multifactorial causes were the most prevalent, accounting for a total of 12 patients (20%), followed by neuroinfection (11%) and autoimmune etiology (10%, including 4 cases of systemic lupus erythematosus and 2 cases of autoimmune encephalitis). Among the remote etiologies, cerebrovascular events were the most frequent (64%). Non-Hodgkin lymphoma of the central nervous system was the main cause of progressive etiologies (2 patients).

Regarding emergent treatment, benzodiazepines were the most frequently used initial treatment (90%), with only two patients not receiving any treatment. As a second-line treatment, phenytoin (77%) and levetiracetam (15%) were the most commonly used anti-seizure medications. In 11 patients, the administration of three medications was necessary, and in two patients, up to four anticonvulsants were administered. The specific dosage and timing of administration were unknown due to the retrospective nature of the study and the lack of this information in the clinical progress notes. The other drugs used are summarized in Table 2. Figure 2 shows the median and interquartile range of the

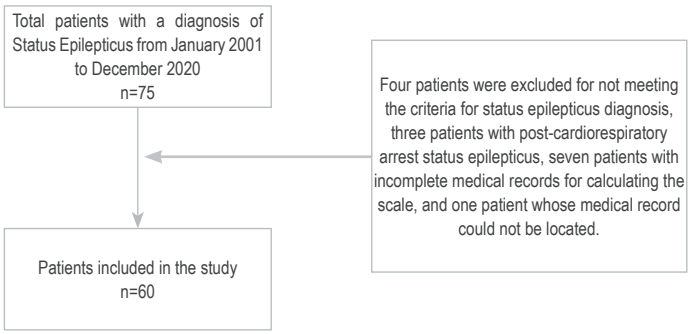

Figure 1. Flowchart of patient selection.

Table 1. Clinical characteristics of the population

Characteristics	Total sample n=60
Sex, n (%)	
Male	14 (23.3)
Female	46 (76.7)
Median age (years range)	49 (30-64)
Etiology of status epilepticus, n (%)	
Acute symptomatic	28 (46.7)
Remote	10 (16.7)
Progressive	8 (13.3)
Unknown	14 (23.3)
Classification of status epilepticus, n (%)	
Generalized convulsive	31 (51.7)
Myoclonic	9 (15)
Focal continuous	8 (13.3)
Non-convulsive	8 (13.3)
Refractoriness of status epilepticus episode, n (%)	
Non-refractory	9 (15)
Refractory	35 (58.3)
Super-refractory	16 (26.7)
Previous epilepsy, n (%)	17 (28.3)
Electroencephalogram during the episode, n (%)	49 (83)
Duration of status epilepticus episode (median)	4 (2-7)
Mortality, n (%)	24 (40)
Duration of hospital stay (median)	12 (7-23.5)
STESS score at diagnosis (median)	2 (2-3)
Comorbidities, n	
Hypertension	12
Connective tissue diseases, n	
Systemic lupus erythematosus	11
Juvenile idiopathic arthritis	2
Inflammatory myopathy	1
Mixed connective tissue disease	1
Type 2 diabetes mellitus	9
Liver cirrhosis	6
End-stage renal disease	6
Post-kidney transplant	4
Hypothyroidism	3
HIV	2
Post-liver transplant	1

Note: Data are presented as median (1Q-3Q) or frequency (%).

Table 2. Specific etiologies of SE and pharmacological treatment employed

Etiology	Number of cases (n=60)
Acute symptomatic (%)	31 (51)
Multifactorial	12
Neuroinfection	7
Autoimmune	6
Metabolic	3
Sepsis	2
Cerebrovascular	1
Toxic	0
Remote (%)	14 (25)
Chronic cerebrovascular	9
Epilepsy	4
Neuroinfection	1
Progressive (%)	4 (6.6)
Mass or tumor	2
Structural	2
Unknown (%)	11 (18.3)
Pharmacological treatment employed	
Initial antiepileptic drug (n, %)	
None	3 (5)
Phenytoin	43 (71.7)
Levetiracetam	11 (18.3)
Valproic acid	1 (1.7)
Lacosamide	2 (3.3)
2nd antiepileptic drug (n, %)	
None	27 (45)
Levetiracetam	2 83.3)
Valproic acid	11 (18.3)
Lacosamide	13 (21.7)
Topiramate	5 (8.3)
Carbamazepine	1 (1.7)
Other	1 (1.7)
3rd antiepileptic drug (n, %)	
None	49 (81.7)
Valproic acid	2 (3.3)
Lacosamide	2 (3.3)
Topiramate	4 (6.7)
Carbamazepine	1 (1.7)
Other	2 (3.3)
4th antiepileptic drug (n, %)	
None	58 (96.7)
Clobazam	2 (3.3)

STESS score when comparing the survivor group (median: 2 points) and the non-survivor group (median: 3 points). In the univariate Cox regression analysis to evaluate the risk of mortality, only the STESS score was found to be statistically significant. The analysis showed that the risk of mortality increased by 38% for each point on the STESS score (B=0.38, HR=1.48, 95% CI: 1.13-1.94, p=0.005) (Table 3).

Discussion

Based on the analysis of our population, generalized convulsive status epilepticus was the most common type, and the majority of cases were refractory to treatment. We found that 24 patients died during their hospital stay, and the main cause within the acute symptomatic classification was multifactorial.

Table 3. Univariate Cox regression analysis to determine the risk of mortality based on various clinical variables in patients with SE.

	Coefficient B	Standard error	Hazard ratio	95% confidence interval		P-value
				Inferior	Superior	
Sex	0.122	0.515	1.130	0.411	3.102	0.8
Age	0.012	0.010	1.012	0.992	1.033	0.2
Previous epilepsy	0.031	0.518	1.032	0.373	2.850	0.9
Duration of episode	0.036	0.036	1.037	0.967	1.112	0.3
Classification of SE						
Generalized convulsive	Referencia					
Focal continuous	0.098	0.792	1.103	0.233	5.211	0.9
Myoclonic	0.799	0.483	2.224	0.864	5.725	0.09
Non-convulsive	0.170	0.671	1.186	0.318	4.415	0.8
Refractoriness						
Non-refractory	Referencia					
Refractory	0.145	0.787	1.156	0.247	5.402	0.8
Super-refractory	1.030	0.761	2.802	0.631	12.447	0.1
STESS score	0.389	0.138	1.476	1.126	1.935	0.005

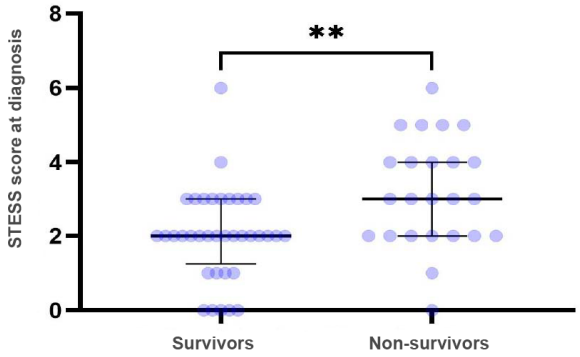

Figure 2. Description: Comparison of STESS scores between survivors and non-survivors. Median and interquartile range are shown; comparisons were performed using the Mann-Whitney U test.

Nearly all patients had comorbidities, with systemic arterial hypertension being the most frequently associated pathology.

According to the univariate Cox regression analysis, the only statistically significant variable was the STESS score, which showed that the risk of mortality increased by 38% for each point on the score (B=0.38, HR=1.48, IC95%:1.13-1.94, p=0.005). This finding is similar to the study by Sandoval et al.[19] conducted in Colombia in 2020, where they found that the ideal cutoff point for the STESS scale was ≥3. In their study, the mortality rate was 33.1%, and 95.6% of patients with a score of <3 survived. Our results, which suggest an optimal cutoff point of ≥3 for discriminating between survivors and non-survivors, align with the original study by Rossetti et al.[20]

Most cases of status epilepticus are due to underlying structural lesions or toxic/metabolic abnormalities.[5,6] In our cohort, the main etiology was previous cerebrovascular events. It is noteworthy that autoimmune pathologies represented a significant subgroup, which may be attributed to our center being a referral center for such conditions. A total of 28% of cases had a previous diagnosis of epilepsy, which is consistent with the findings of various authors who report that up to 10% of adults experience one or more episodes of status epilepticus in their lifetime.[6,13,16] Acute symptomatic causes continue to be the main cause in the majority of reported studies, as in our population.[2,21]

Convulsive status epilepticus (including generalized, focal continuous, and myoclonic) accounted for nearly 80% of the included patients, which could be attributed to the underdiagnosis of non-convulsive status epilepticus, as previously reported.[11,13,21]

We found a high percentage of refractory cases (RSE and SRSE), accounting for 85% of cases, with an overall mortality rate of 40%. As reported in the literature, the mortality associated with this condition ranges from 16% to 20%, with wide variation depending on the underlying etiology,[7-10] reaching 69-81% in post-anoxic status epilepticus.[10,14,15] The high mortality is attributed to multiple associated complications, such as arrhythmias, hypoventilation and hypoxia, aspiration pneumonia, and neurogenic pulmonary edema.[21,22] The mortality rate in RSE varies from 19% to 60% according to several articles.[22,23,24]

The median duration of status epilepticus was 96 hours, similar to the findings of the study by Ramos et al.,[25] where the mean duration was 101 hours and the in-hospital mortality rate was 38%, which is consistent with our cohort. The most common emergent treatment was with benzodiazepines, and phenytoin followed by levetiracetam were the most frequently used as initial urgent treatment, which is in line with international guidelines.[5]

Regarding the STESS scale in our population, we confirmed its association with in-hospital mortality, with an optimal cutoff point of ≥3. This is consistent with the original study[20] conducted with a series of 34 patients, which reported a negative predictive value (NPV) of 0.94 and an area under the curve of 0.75. In comparison, our results showed an NPV of 82.76 and an area under the curve of 0.72. According to the cutoff point of ≥3, the NPV was high, and the positive predictive value was low, indicating that the STESS scale reliably identifies survivors rather than non-survivors, consistent with other external validation studies.[27] Although the cut-off point of ≥3 had the best discrimination, the NPV for mortality was higher with lower scores (≥1 and ≥2). This finding is valuable, particularly because the reliable identification of survivors may be the most important application of the scale in clinical practice. The cut-off point of ≥3 was chosen because it has high sensitivity and an appropriate NPV, which helps identify patients with status epilepticus, reducing the number of false negatives rather than false positives and ensuring that no patients at risk are missed.

The limitations of this study include its retrospective observational design and its confinement to a single tertiary care center, which may differ from other healthcare centers due to the higher concentration of complex pathologies (autoimmune, HIV, solid organ, and bone marrow transplant recipients, among others) treated at our center. Additionally, the study only included adults, and there was no follow-up of patients after their hospital discharge. Another significant limitation is the lack of sample size calculation.

Conclusions

The STESS scale is significantly associated with in-hospital mortality and can be used as a predictor of adverse outcomes in patients with SE with a cutoff point of ≥3, regardless of its cause, even in settings where the population presents a higher number of concomitant metabolic conditions, as in the case of our center.

Based on our study, we can conclude that hospital mortality was higher than in other studies reported in the literature, with acute symptomatic forms as the leading cause, which may be related to the type of hospital and the conditions it treats.

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