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Predictors of high functional disability and mortality at 3 months in patients with status epilepticus

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ABSTRACT

Purpose: There are differences in epidemiology, etiology, and outcome in status epilepticus (SE) between developing and developed countries, which limits generalizability. We evaluated factors related to outcome at 3 months in SE patients in a developing country- Ecuador.

Methods: Retrospective analysis of a prospectively collected dataset of patients treated for SE at a single hospital over 4 years, recording on 107 patients and 109 episodes, including clinical, demographic, and prognosis assessments.

Results: Hospital mortality was 33%, and 38% at 3 months. Glasgow Coma Scale score pretreatment ≤12 (odds ratio = 7.7), Charlson Index of comorbidities ≥3 (odds ratio = 5.6) and brain lesion (odds ratio = 6.4) predicted high disability. History of epilepsy was associated with favorable outcome in general, and showed a positive impact on survival rates (odds ratio = 0.3), while Glasgow Coma Scale scores pretreatment ≤12 (odds ratio = 4.1) and refractory SE (odds ratio = 2.1) were associated with reduced survival rates. Acute symptomatic etiology was the most common cause of SE (58%). Etiologies with structural brain lesion showed a significantly lower survival rate (Log ranks = 0.04 and 0.003) compared to other groups.

Conclusion: Mortality rate at 3 months for SE patients was high. Glasgow Coma Scale, Charlson Index, and brain lesions were associated with unfavorable outcome, including mortality. Overall, the results were similar to those reported in more developed countries, but some differences, including overall higher mortality, prevalence of nonconvulsive SE, and lack of association of age with outcome were evident.

1. Introduction

Status Epilepticus (SE) is well-recognized as a common neurological emergency associated with high morbimortality and health care costs [1]. Despite the improvement in care, neuromonitoring, and new intravenous antiepileptic drugs, the mortality rate of patients with convulsive SE can reach as high as 39% [2].

There appear to be differences in epidemiology, etiology, and outcome in SE between developing and developed countries. A meta-analysis suggested a higher mortality rate in developing countries than developed nations (2.92 vs 0.98 per 100,000 person-years) [3]. However, regarding factors related to mortality in SE, the vast majority of available data originates from developed nations [4]. For example, incidence, common etiologies, disability, and mortality rates of SE in Central and South American nations are poorly defined [5]. In addition, clinical studies which focus on factors predictive of outcome in such contexts are scarce [6–8], with most reports comprised of descriptive analysis, or a focus on specific SE etiologies.

Multiple factors have been associated with an increase in mortality risk of patients with SE. Glasgow Coma Scale scores upon presentation, age, underlying etiology of SE, and comorbidities are well-recognized factors [9–12]. Although all these have been demonstrated in developed countries, such populations have different characteristics and health care contexts, when compared with developing nations.

Thus, there is a need for projects to define the epidemiology, etiologies and factors related to unfavorable outcome from SE in developing countries. Such reports would aid the development of strategies to improve the care systems pertaining to patients with SE. An improved understanding of etiologies and risk/protective factors operating on clinical samples in developing countries would potentially also advance medical SE treatment in general, including in developed countries; for example, in the treatment of immigrant populations. As such, the aim of

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this study is to evaluate factors related to SE outcome at three months in patients in Ecuador, a developing nation in South America. We hypothesized that the factors described above, from research on SE in developed countries, would also be associated with SE outcome in our sample from Ecuador.

2. Patients and methods

A cohort study was conducted, with all of the variables collected prospectively, and the analysis performed retrospectively, on our database of SE cases from November 2015 to January 2020 at Eugenio Espejo Hospital. This is a large (over 350 beds), urban, public healthcare and teaching center, associated with a large state-run university. It is located in Quito, the capital city of Ecuador. Services include emergency rooms, operating theaters, community medicine programs, epidemiology, and specialists including both neurology and neurosurgery. The aim of this study was to evaluate the factors related to outcome at three months in Ecuadorian patients with SE. A total of 112 SE patients was recorded in the target time frame.

2.1. Inclusion and exclusion criteria

Inclusion criteria were: age 16 or older, diagnosis of SE according to the International League Against Epilepsy (ILAE) definition proposed in 2015 [13], or diagnosis of non-convulsive SE (NCSE) according Salzburg criteria [14]. Patients were excluded if they could not be followed up after hospital discharge. With such inclusion and exclusion criteria, of the total 112 patients, 107 individuals who experienced 109 SE episodes were included. All these 107 were followed up (external clinic department at Eugenio Espejo Hospital) at least twice, at three months after hospital discharge.

2.2. Definitions and variables measured

Status epilepticus type, convulsive or nonconvulsive, was considered according to the ILAE definition and Salzburg criteria, respectively [13,14]. Best level of consciousness according to the Glasgow Coma Scale [15] at onset of SE in the post-critical period was recorded. Demographic information was recorded, particularly relevant for the current research is age of the patient. Presence of symptoms at the initial neurological evaluation by a neurologist were categorized as: seizure, disorder of consciousness (somnolence, stupor, or coma), seizure plus disorder of consciousness (patients with a sustained diminished level of consciousness after one hour from last seizure), focal neurologic deficits (permanent neurological deficit due to structural cerebral lesion, not including Todd's paralysis), delirium (patients with fluctuations of level of consciousness and periods of agitation), or other (e.g., aphasia, behavior disorders, psychiatrics symptoms). Prognostic scores such as Status Epilepticus Severity Score (STESS) [16] were recorded (as this is the scale most commonly used in the extant literature on SE), as were comorbidities as registered according to the Charlson Index [17]. In addition, information regarding structural brain lesions demonstrated by computed tomography (CT) or/and magnetic resonance image (MRI) was collected. Only CT and MRI scans were performed on 23 and 15 patients respectively, and 69 patients were assessed with both radiological methods. Radiological contrast (iodine-base contrast for CT, and gadolinium for MRI) was applied according to the suspected diagnosis or on the neuroradiologist's recommendations. Refractory SE was defined as lack of response to at least two standard lines of antiepileptic drugs [18].

2.3. Etiology

Etiology of SE was considered according to the guidelines of the ILAE Commission for Classification and Terminology of Epilepsy [19] and by groups as: structural lesion (cerebrovascular disease, anoxic/hypoxic lesion, traumatic brain injury, tumor); metabolic (hydroelectrolytic disorders, hypoglycemia, uremia, hepatic failure, toxic); immune (autoimmune encephalitis, autoimmune systemic disease with evidence of autoimmune-mediated central nervous system inflammation); central nervous system (CNS) infections; epilepsy history (triggered by poor compliance to antiepileptic drugs, mild viral/bacterial/parasitic infections, sleep deprivation, toxic and hydroelectrolytic disorders); multiple concomitant cause (two or more likely acute etiologies were present at the same time); and unknown causes. Acute symptomatic etiology was defined in patients with SE with close temporal association with an acute CNS insult (structural lesion), and/or a systemic, metabolic, infectious, or toxic cause of a cerebral dysfunction.

Additionally, the etiologies were grouped in cases with a structural brain lesion demonstrated by CT or MRI, as follows: Group 1 - cases with a structural focal brain lesion demonstrated by CT or MRI, as cerebrovascular disease, anoxic/hypoxic lesion, CNS neoplasm and traumatic brain injury; Group 2 – cases with non-focal structural cerebral lesion, as metabolic, CNS infection, autoimmune and degenerative diseases, and Group 3 - epilepsy (including remote and symptomatic causes) and unknown (no defined etiology).

2.4. Treatment protocol and outcome

All patients were treated according to our institutional protocol, shown in Fig. 1. This follows the guidelines of SE treatment proposed by the Neurocritical Care Society [20]. The anesthetic drug was selected according to the comorbidities, suspected etiology, clinical signs of the patient, and preference of the intensive care specialist. Electroencephalography (EEG) was performed in the first 2 h of the patient being admitted to hospital. These had 60–120 min duration of recording, with the study guiding the minor doses of anesthetic drugs to obtain a burst suppression pattern or avoid the patterns related with NCSE. In the following 24 h, antiepileptic drugs including levetiracetam, valproic acid, clobazam, or clonazepam and lacosamide were introduced with increasing doses. EEG (60–120 min. duration) was repeated every 24 h, and doses of anesthetic drugs were gradually diminished during the EEG monitoring. If subtle seizure (clonic, myoclonic, gaze forced deviation, etc.) and/or NCSE patterns were observed, doses of anesthetic and antiepileptic drugs were increased. Conversely, if clinical signs and EEG indicated control of SE then anesthetics drugs were gradually reduced over the next 24 to 36 h with another EEG performed before total withdrawal. Doses of anesthetic drugs were always adjusted or removed during the daily EEG monitoring. In all patients, daily EEG (60–120 min. duration) was conducted until 72-h seizure free, and without NCSE patterns, or return to previous SE consciousness state without clinical signs of seizure.

Rankin score was used to evaluate outcome [21]. It was applied at hospital discharge and at three-month follow-up. Rankin scores 0–3 were considered as 'survival and favorable outcome', 4–5 were considered as 'survival with high disability', and 6 indicated mortality.

2.5. Statistical analysis

Data are summarized as mean ± standard deviation (SD) and range for continuous variables, and as frequency for categorical variables. Bootstrapping was used to calculate 95% confidence interval (95%CI) ranges. Univariate binary logistic regression was used to identify factors predictive of favorability of outcome, and in those who were survivors at three months, predictors of high disability. Stepwise binary logistic regression was used to identify independent predictors of favorability of outcome and high disability in survivors. Cox regression was used to evaluate variables predictive of survival rate up to the three-month follow-up. For tests of statistical significance, a p value threshold and log ranks of 0.05 were employed. Odds Ratios were estimated for magnitude of effect, with 95%CIs. Kaplan-Meier curves were constructed according to etiological groups to evaluate rate of survival at

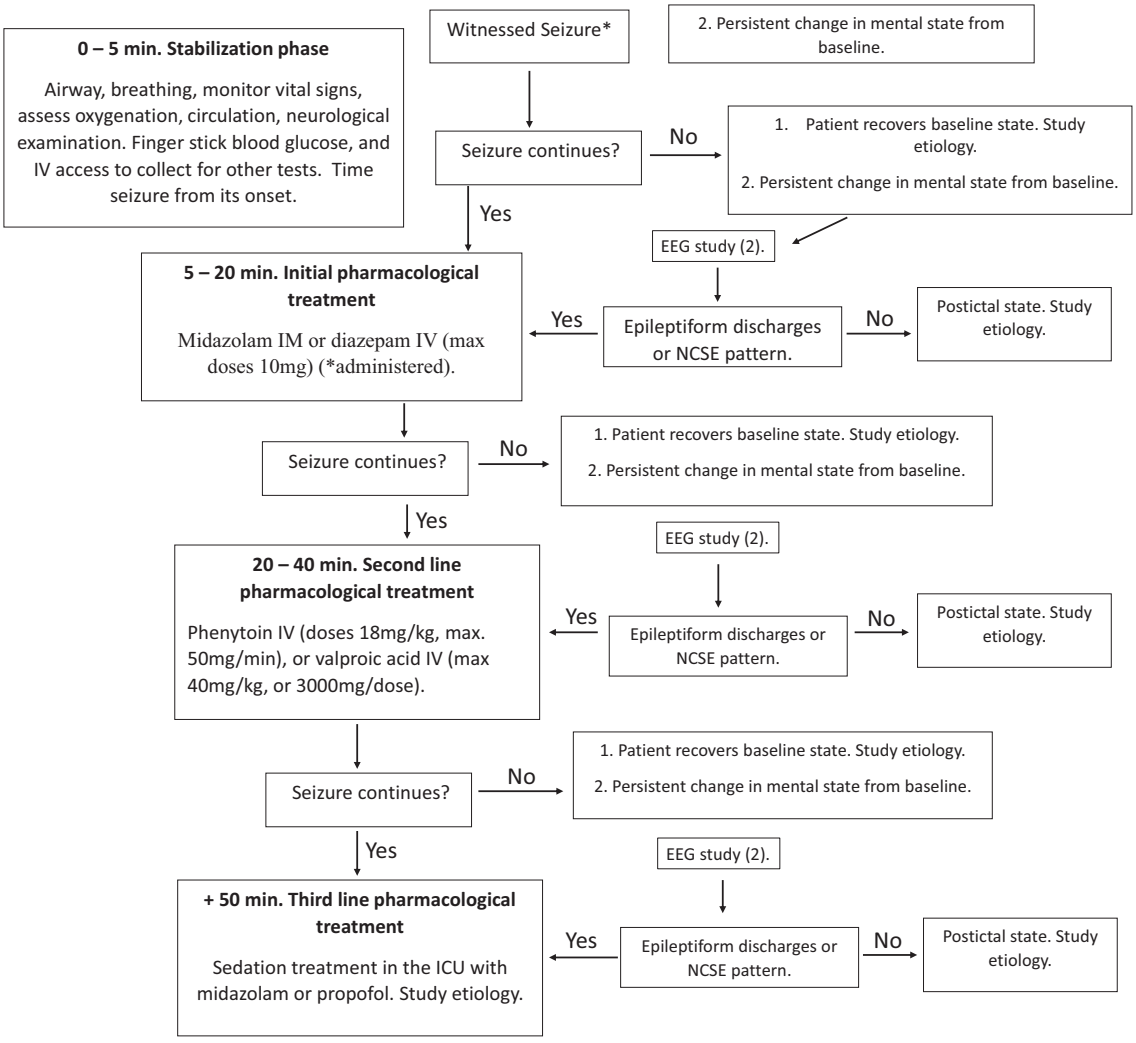

Fig. 1. The treatment protocol.

three months. For statistical analyses, IBM SPSS 20.0 software for Windows was used.

2.6. Ethical approval

The ethical principles put forth in the 1964 Helsinki declaration were followed. Informed consent was obtained from all individual participants included in the study or their relatives in instances of altered judgment or impaired level of consciousness. The personal data of all patients were protected. The execution of this study was approved by the institution's research ethics committee.

3. Results

3.1. Demographic and clinical features

A total of 107 different patients were enrolled during the study period and 109 SE episodes were registered. Demographic and clinical features of the patients who suffered these 109 SE episodes are shown in Table 1. Mean age of the patients was 47.6 ± 23.5 years with a male predominance 64/109 (59%). Convulsive SE was the most common variant recognized, in 91/109 (84%) of cases. Seizure and disorders of consciousness were the most frequent initial symptoms, with rates of 43/109 (39%) and 28/109 (26%) respectively. Acute symptomatic etiology was identified in 63/109 (58%) of cases and refractory SE was recognized in 62/109 (57%). Healthcare-associated infections were a frequent complication, occurring in 56/109 (51%) of cases. Hospital mortality was 36/109 (33%) of cases and mortality at three months extended to 41/109 (38%) of cases. Five patients were excluded, because they were not available for their three-month follow-up appointments, and final outcome was not evaluated. The age range of these patients was 22–46 years. In three cases the SE etiology was epilepsy, for one it was cerebrovascular diseases, and the other traumatic brain injury. All survived to hospital discharge.

3.2. Predictors of unfavorable outcome

Of the 109 episodes of SE, 46 (42%) were considered to have a favorable outcome at three months (i.e., survival and low disability based on Rankin scores). Table 2 shows the results of binary logistic univariate analyses of different demographic and clinical variables as predictors of unfavorable outcome at three months (i.e., Rankin scores = 4–6 / high disability or death) compared to favorable outcomes (i.e., Rankin scores 0–3 / no or low disability). A history of epilepsy was a significant protective factor against unfavorable outcome (odds ratio = 0.3). In contrast, significant risk factors for unfavorable outcome were pretreatment Glasgow Coma Scale scores ≤12 (odds ratio = 10.6), STESS scores ≥4 (odds ratio = 5.7), comorbidities on the Charlson Index ≥3 (odds ratio = 5.8), and brain lesion observed on CT or MRI (odds ratio = 3.2).

Table 1
Demographic and clinical features of 109 episodes of status epilepticus.

Demographic and Clinical Features		Mean (±SD) / Count (%)	95%CI
Age		47.6 (±23.5)	43.6–51.9
Male		64 (58.7%)	50–68%
Previous medical history			
	Epilepsy	29 (26.6%)	18–35%
	Intracerebral hemorrhage	5 (4.6%)	1–9%
	Ischemic stroke	6 (5.5%)	2–10%
	Cerebral palsy	6 (5.5%)	2–10%
	Alcoholism	4 (3.7%)	1–7%
	Neoplasm [1]	11 (10.1%)	5–17%
	HIV	1 (0.9%)	0–3%
	Chronic kidney disease	7 (6.4%)	2–12%
Status Epilepticus	Convulsive	91 (83.5%)	76–91%
	Nonconvulsive	18 (16.5%)	9–24%
Initial symptoms	Seizure	43 (39.4%)	31–49
	Disorder of consciousness	28 (25.7%)	17–34%
	Seizure plus disorders of consciousness	24 (22.0%)	15–30%
	Focal neurological deficit	6 (5.5%)	2–10%
	Delirium	4 (3.7%)	0–7%
	Others	4 (3.7%)	1–7%
Glasgow Coma Scale pretreatment		10.9 (±3.6)	10.3–11.6
Acute symptomatic etiology		63 (57.8%)	49–67%
STESS		2.3 (±1.4)	2.1–2.6
Refractory SE		62 (56.9%)	48–65%
Charlson Index (comorbidities)	0–1	44 (40.4%)	31–50%
	2	26 (23.9%)	17–32%
	3 +	39 (35.8%)	27–45%
Health care associated infections		56 (51.4%)	42–61%
Hospital stay (days)		27.2 (±29.3)	22.2–33.2
Outcome	Favorable outcome at 3 months	46 (42.2%)	33–51%
	High disability at 3 months	22 (20.2%)	14–28%
	Hospital mortality	36 (33.0%)	24–42%
	Mortality at 3 months	41 (37.6%)	28–47%

STESS = Status Epilepticus Severity Score; SE = Status Epilepticus. [1] Neoplasm included systemic and cerebral neoplasm.

Many of these factors, though predictive when considered in isolation in univariate analyses, may be interrelated. To identify the set of statistically significant independent predictors of unfavorable outcome (as opposed to favorable outcome) we performed a binary logistic regression with forward stepwise conditional entry of independent variables into the model. For entry into the model, the significance threshold was 0.05, and for removal it was 0.10. The variables considered were all those shown in Table 2 to have been predictors of unfavorable outcome at $p \leq .10$ (i.e., history of epilepsy, Glasgow Coma Scale score ≤ 12, refractory SE, STESS score ≥ 4, Charlson Index ≥ 3, and brain lesion evident on CT/MRI). A threshold for inclusion of 0.10 observed in the univariate analyses was selected as this will include any variables that showed a trend for significance (i.e., p values between 0.05 and 0.10) and which may be significant at the model entry threshold when considered in the multivariable analysis. This produced a final significant model predicting unfavorable outcome, X^2 (df = 3) = 50.74, $p <$ .01, with a Cox & Snell R^2 of 0.37. Within the model, only three factors were independent predictors of unfavorable outcome. These were: previous epilepsy as a protective factor, odds ratio = 0.31 (95%CI = 0.11–0.85), $p = .02$, and as risk factors, Glasgow Coma Scale equal to or less than 12, odds ratio = 12.8 (95%CI = 4.5–36.4), $p < .01$, and finally comorbidities on the Charlson Index equal to or greater than 3, odds ratio = 6.3 (95%CI = 2.0–19.7), $p < .01$. The same pattern of results was found with backward conditional entry of variables.

3.2.1. *Predictors of disability in SE survivors*

At three-month follow-up there were 68 survivors (Table 2). Of these, 46 (68%) had no or low disability (Rankin scores 0–3) and 22 (32%) had high-disability (Rankin scores 4–5). Significant predictors of high disability at three months were Glasgow Coma Scale scores ≤12 (OR = 7.7), Charlson Index score ≥ 3 (OR = 5.6), and brain lesions observed on CT or MRI (OR = 6.4).

The same method of analysis was used to identify a set of independent predictors of high disability among the SE survivors. That is, binary logistic regression with forward conditional entry of any variables identified in the univariate analyses shown in Table 2 as being predictive of disability at $p \leq .10$ (Glasgow Coma Scale, STESS, Charlson Index, and brain lesion evident on CT/MRI). Again, criterion for model entry was $p < .05$ and for removal $p > .10$. This produced a significant final model predicting high disability among the 68 survivors of SE, X^2(df = 2) = 19.41, $p < .01$, with a Cox & Snell R^2 of 0.25. Only two factors were significant independent predictors of high disability in the final model: Glasgow Coma Scale score ≤ 12, odds ratio 6.7 (95%CI = 2.0–22.3), $p <$ .01, and Charlson Index scores equal to or greater than 3, odds ratio = 4.6 (95%CI = 1.3–16.6), $p = .02$. Backwards conditional entry of

Table 2
Univariate analysis using binary logistic regression of factors related to outcome at three months in patients with status epilepticus.

	All episodes				Survivors only			
	Favorability of outcome				Disability			
	Favorable (%)	Un-favorable (%)	OR (95%CI)	p^1	High Disability (%)	Low Disability (%)	OR (95%CI)	p^2
n	46	63			22	46		
Age > 65	12 (26)	18 (29)	1.1 (0.5–2.7)	0.77	6 (27)	12 (26)	1.1 (0.3–3.3)	0.92
Epilepsy history	27 (59)	19 (30)	0.3 (0.1–0.7)	**<0.01**	10 (45)	27 (59)	0.6 (0.2–1.6)	0.31
Glasgow Coma Scale ≤12	10 (22)	47 (75)	10.6 (4.3–26.0)	**<0.01**	15 (68)	10 (22)	7.7 (2.5–24.1)	**<0.01**
Seiz. + Dis. Consc.	8 (17)	15 (24)	1.5 (0.6–3.9)	0.42	3 (14)	8 (17)	1.3 (0.3–5.6)	0.70
Nonconvulsive SE	8 (17)	10 (16)	1.1 (0.4–3.1)	0.83	1 (5)	8 (17)	4.4 (0.5–37.8)	0.18
Acute symptomatic	24 (52)	39 (62)	1.5 (0.7–3.2)	0.31	14 (64)	24 (52)	1.6 (0.6–4.6)	0.38
Refractory SE	22 (48)	40 (63)	1.9 (0.9–4.1)	0.10	11 (50)	22 (48)	1.1 (0.4–3.0)	0.87
STESS ≥4	3 (7)	18 (29)	5.7 (1.6–20.9)	**<0.01**	5 (23)	3 (7)	4.2 (0.9–19.6)	0.07
Charlson Index ≥3	7 (15)	32 (51)	5.8 (2.2–14.8)	**<0.01**	11 (50)	7 (15)	5.6 (1.7–17.8)	**<0.01**
Brain lesion	30 (65)	54 (86)	3.2 (1.3–8.1)	**0.01**	20 (91)	28 (61)	6.4 (1.3–30.9)	**0.02**

p^1 value = Unfavorable outcome (Rankin 4–6) with the reference Favorable outcome (Rankin 0–3); p^2 value = Disability (Rankin 4–5) with reference Favorable outcome (deceased patients excluded); bold = statistically significant association. OR = odds ratio; 95%CI = 95% confidence interval of the odds ratio; Glasgow Coma Scale = Glasgow Coma Scale score pretreatment; Seiz. + Dis. Consc. = Seizure plus disorders of consciousness as initial symptom. SE = Status Epilepticus. Brain lesion = brain lesion demonstrated by radiological studies (CT or MRI).

variables produced the same pattern of results.

3.3. Survival analysis

Cox regression analysis was used to investigate how clinical and demographic variables related to survival time, measured to three-months post-episode. The significance threshold here was set at 0.05. This is summarized in Table 3. History of epilepsy (odds ratio = 0.3) showed a statistically significant positive impact on survival. In contrast, Glasgow Coma Scale scores (odds ratio = 4.1), refractory SE (odds ratio = 2.1) and STESS scores (odds ratio = 2.1) were significantly associated with reduced survival rate at three months.

The relationship between etiology and mortality was also examined, with results shown in Fig. 2. Epilepsy decompensation by noncompliance with antiepileptic drugs or other trigger factors (26/109, 24%), cerebrovascular disease or anoxic hypoxic lesion (26/109, 24%), and multiple concomitant etiology (15/109 14%) were the most common causes of SE. These last two etiologies (cerebrovascular disease or anoxic hypoxic lesion and multiple concomitant etiology) were the disorders with the highest fatality rates at 62% and 80%, respectively. Univariate binary logistic regression on mortality for all of the etiology groups are summarized in Table 4. In these analyses, the reference category is epilepsy as the etiology underlying the SE episode. These confirmed that both of the categories cerebrovascular disease / anoxic hypoxic lesion, and multiple concomitant etiology, when compared to SE resulting from epilepsy, were significantly more likely to be associated with mortality at three months.

Kaplan-Meier curves were produced and are shown in Fig. 3. These confirmed the negative impact on survival rate at three months for patients with etiologies related to structural focal brain lesion demonstrated on CT or MRI (Group 1) vs epilepsy/cryptogenic causes (Group 3) (Log rank <0.01), and versus etiologies with non-focal structural brain lesion (Group 2) (Log rank = 0.04). There was a nonsignificant difference between those two (Log rank = 0.29).

4. Discussion

Status epilepticus (SE) is a common neurological emergency with a high rate of morbidity and mortality. The reported fatal outcome described in different studies in adults varies from 2% to 46%, and may be as high as 57%, when considered over longer periods [3,22]. As with most medical research, which focuses on populations in high-income countries, there is disproportionately little research on critical care medicine in South American populations [23]. Within the region, most studies of SE have provided a descriptive analysis of data, and only one evaluated factors associated with short term mortality [6–8]. In our cohort, the rate of hospital mortality reached 33%, and at three months extended to 38% of patients. This level of SE mortality is broadly comparable to existing studies from around the world [22,24,25]. For example, our reported rate of hospital mortality at 33% is similar to that reported on a study of Brazilian patients with SE, where the figure was 36% [8].

Data from more than 30 studies were analyzed in a systematic review with meta-analysis [26] which reported an overall mortality rate in SE for adults at 16% in high-income countries. Clearly, this is less than half of the mortality rate described in our Ecuadorian sample. Nevertheless, relatively low rates of mortality in high-income, developed countries, compared to developing countries, are not consistently observed. An analysis of SE mortality in Italy reported that their cohort suffered 33% mortality by 30 days [27]. Furthermore, a review of clinical studies on SE found that mortality rates in adults varies greatly across study samples, between 0 and 40% for short-term mortality, and 0 and 57% for long-term mortality. Notably, that substantial variation was mainly evident because of study cohorts from developed countries [22].

Overall, according to our results, and our review of the limited existing clinical data, it seems likely that there is higher mortality from SE in developing countries, compared to developed countries. However, in the opinion of the authors, strong evidence to confirm this is still lacking. Heterogeneity of study samples, difference in definitions of SE and refractory SE, and scarcity of data from developing countries are some of the factors that prohibit a conclusion on the issue [28,29]. It may be that due to the heterogeneity of clinical presentations across populations, analyses may need to be adjusted by SE severity (e.g., STESS, or Epidemiology-based Mortality Score in Status Epilepticus - EMSE scores), age, etiology, structural brain lesions, and latency to start antiepileptic treatment, if true difference in mortality between developed and developing countries are to be reliably identified [30].

Lack of treatment, previous hospital admission, longer periods of SE, non-availability of continuous neuromonitoring, unreliable availability of newer antiepileptic drugs, and absence of established treatment protocols are some proposed factors that compromise outcome of SE in developing countries. However, it should be acknowledged that cohort studies carried out in European samples have demonstrated that deviation from treatment guidelines does not impact SE prognosis [31]. Similarly, the use of newer antiepileptic drugs may not modify final outcome [32,33].

Epidemiological studies to evaluate long-term mortality in developing nations, using uniform definitions of SE and refractory SE, are sorely needed. Identification of clinical variables impacting on outcome in our populations would aid clinical diagnosis and management. In addition, understanding of the interactions of such variables in our resource-limited environments are required in order to develop efficacious strategies to improve the care system of patients with SE.

In our cohort, level of consciousness (Glasgow Coma Scale scores ≤12), refractory SE, and severity of SE according to STESS were factors significantly associated with mortality at three months. Etiologies including cerebrovascular diseases plus anoxia/hypoxia status post cardiac arrest and multiple concomitant etiologies were the main contribution to mortality. These findings are similar to those previously reported for an Italian cohort of SE patients [27]. Regarding our classification of multiple concomitant etiology, this included patients with metabolic and septic complications, and likely included patients with metabolic disorders. These aspects should be taken into account when interpreting our results. Poor outcome in acute metabolic disturbance related SE is well-recognized, with fatality or permanent supportive care required in up to 65% of cases [29]. Cerebrovascular disease is similarly recognized as another cause related to high morbidity and mortality. One study reported a 57% level of long-term mortality, with a doubling of the risk of death at 6 months [34], similar to our findings.

In contrast, history of epilepsy in SE patients was associated as a protective factor against mortality at three months. Similar findings have been found by other authors [29,35]. In our study, the majority of

Table 3
Cox regression of factors associated with reduced survival rate at three months in patients with status epilepticus.

	OR	95%CI	*p*
Age > 65 years	1.5	0.7–3.0	0.28
Epilepsy history	0.3	0.1–0.7	**<0.01**
Glasgow Coma Scale pretreatment ≤12	4.1	2.0–8.7	**<0.01**
Initial symptom Seizure + Dis. Consciousness	1.1	0.6–2.0	0.88
Nonconvulsive SE	1.1	0.5–2.4	0.76
Acute Symptomatic	1.1	0.6–2.1	0.75
Refractory SE	2.1	1.1–4.3	**0.03**
STESS ≥4	2.1	1.1–4.3	**0.03**
Charlson comorbidities index ≥3	1.5	0.8–2.9	0.26
Brain lesion	2.3	0.9–6.1	0.08

p value = Patients who died (Rankin 6) with the reference survival patients (Rankin 0–5); OR = odds ratio; bold = statistically significant association, 95% CI = 95% confidence interval of the odds ratio; Glasgow Coma Scale = Glasgow Coma Scale score pretreatment; Seiz. + Dis. Consc. = Seizure plus disorders of consciousness as initial symptom. SE = Status Epilepticus. Brain lesion = brain lesion demonstrated by radiological studies (CT or MRI).

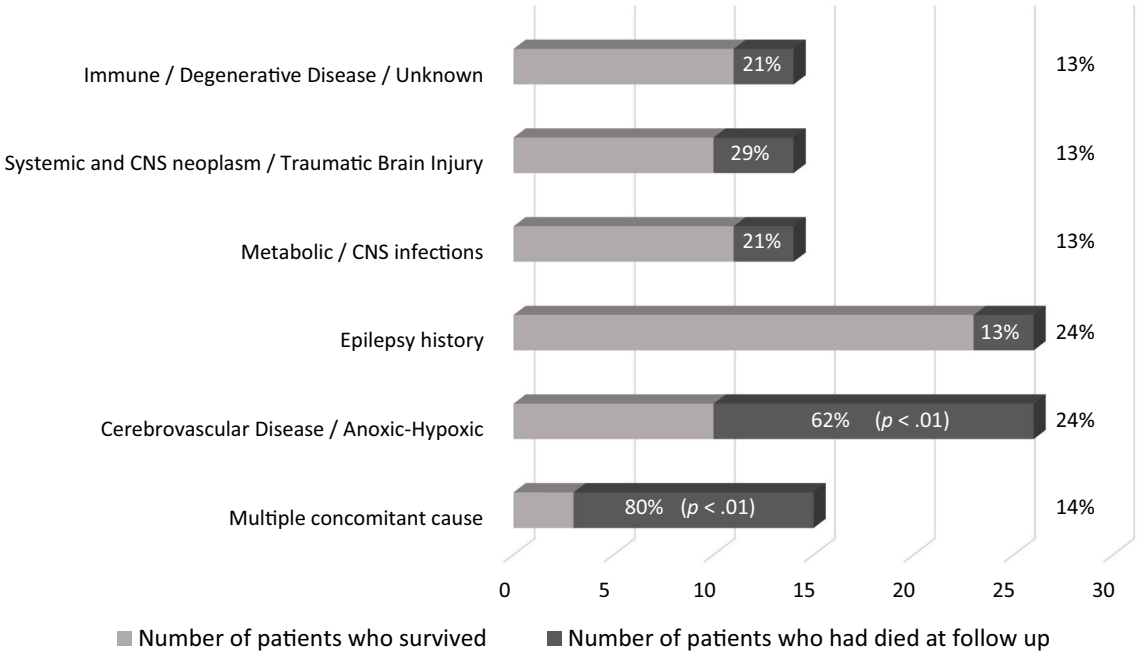

Fig. 2. Mortality rate of status epilepticus episode (white text) and etiology as percentage of all cases (black text).
p values refer to the increased risk of mortality compared to patients with epilepsy history (see Table 4).

Table 4
Univariate binary logistic regression of etiologies (versus epilepsy) related to mortality at three months in patients with status epilepticus.

Etiologies[1]	OR	95%CI	*p*
Immune / Degenerative disease / Unknown	2.1	0.4–12.1	0.41
Systemic and CNS neoplasm / Traumatic brain injury	3.1	0.6–16.3	0.19
Metabolic / CNS infections	2.1	0.4–12.1	0.41
Cerebrovascular disease / Anoxic-hypoxic	12.3	2.9–51.7	**<0.01**
Multiple concomitant cause	30.7	5.4–175.8	**<0.01**

OR = odds ratio; 95%CI = 95% confidence interval of the odds ratio; Etiologies[1] reference epilepsy etiology; Cerebrovascular Dis = Cerebrovascular Diseases; CNS = Central nervous system; Immune = Autoimmune Diseases.

SE episodes in epileptic patients were trigged by low antiepileptic drug adherence, alcohol consumption, infections, and hydroelectrolytic disorders. Existing evidence suggests that age is related to mortality in SE, but this was not observed in our sample. The cohort included here were mainly patients under 60 years of age, which could be the reason for our divergent results. Relatively young patients is a feature of all studies carried out in Central and South America, and India [4,6–8]. The reason for the lower age is unclear, but probably related to the generally lower mean population age in developing countries, compared to more developed countries, particularly within the demographic of people relying on public health care. This is probably one of the patient characteristics that is a distinctive factor of clinical care in most developing countries. However, history of epilepsy was not found to be a protective factor against disability among survivors, which may be because of the low number of patients in the analysis with high disability. A further point is that we did not account for previous basal disability of patients. It may be that aggravation of basal Rankin scores is a more appropriate method of analysis to identify differences among survivors.

In general terms, our findings are in accordance with prognostic factors related to mortality demonstrated in studies carried out in more developed nations. Exceptions to this are, in addition to age, the lower reported prevalence of nonconvulsive SE in the current study, and prolonged length of hospital stay of patients. Lack of continuous EEG neuromonitoring is an important issue that likely links the last two

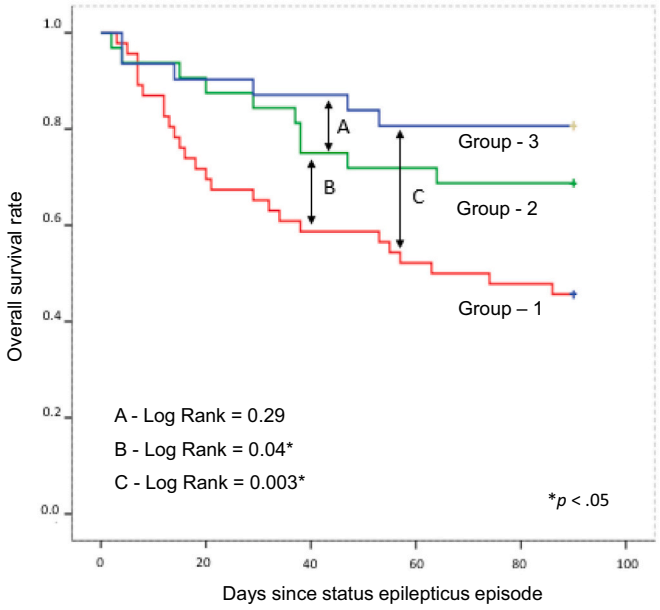

Fig. 3. Kaplan-Meier analysis according to different grouped-etiology classifications.
Etiologies with structural focal lesion are: Group 1 (cerebrovascular diseases, anoxic/hypoxic, CNS neoplasm, and traumatic brain injury). Patients with non-focal structural cerebral lesion are: Group 2 (metabolic, CNS infections, immune diseases or degenerative diseases). Group 3 comprises epilepsy, including remote and symptomatic causes and unknown etiology.

mentioned characteristics. In our opinion it is a challenge to avoid overtreatment in our daily clinical practice, when operating with limited access to resources. This could explain the high frequency of nosocomial infections and complications (e.g., hypotension, shock, organ failure, etc.) and may contribute to excess mortality. Nevertheless, this is merely our impression, and requires future study to elucidate the different factors implicated in SE mortality in developing countries.

On the other hand, clinical studies that include factors predictive of mortality rate in SE, and also evaluate favorability of outcome and functional disability in survivors, are scarce. Factors associated with disability are poorly understood [9]. The first investigations to assess outcome in SE were only conducted in the last two decades of the past century. Poor outcome was identified in 11 and 12% of patients of cohort studies [36,37]. One study reported a 23% rate of disability according to Glasgow outcome scores at hospital discharge in 74 patients with SE [9], a finding comparable to that observed in the current study. The variables related to high disability in this study were disorders of consciousness (Glasgow Coma Scale score pretreatment $\leq$12), Charlson Index of comorbidities $\geq$3, and brain lesion demonstrated by CT or MRI. However, stepwise modelling of factors suggested that Glasgow Coma Scale of level of consciousness (pretreatment) and Charlson Index of comorbidities scores were the only independent predictors of high disability. When we used the same method to identify predictors of unfavorable outcome (i.e., high disability or death), the same two factors emerged, however, in this analysis, a previous diagnosis of epilepsy emerged as a third independent factor, in this case a protective factor. A previous study recognized that acute symptomatic seizure increased length of hospitalization and predicted functional disability [9].

A further observation is that scores used to evaluate severity of SE (STESS $\geq$4) demonstrated a significant association with outcome at three months in the univariate analyses. The clinical application of severity scores has been shown to serve a valuable role in prediction of outcome in limited resource settings, such as in South American hospitals [38,39]. Unfortunately, to our knowledge, no other research has evaluated factors associated with disability in an adult population after survival of an SE episode in developing countries.

4.1. Limitations

A limitation of this study is its observational single-center design and a relatively small sample. For this reason, we could not adjust statistical analysis by factors that differ between our cohort and those in other published studies. The overrepresentation of patients mainly under 60 years likely explains why we found no relation between mortality and patient age. Another important point to take into account is that Eugenio Espejo Hospital, where the research was conducted, is a tertiary care center and our sample likely has an overrepresentation of refractory SE patients. This factor may have contributed to raised levels of mortality and disability. Our findings should be confirmed with larger samples and multicenter studies.

5. Conclusions

Status epilepticus was found to have a high morbidity and mortality at three-month follow-up in Ecuadorian patients. High STESS scores and brain lesions were associated with high disability at 90 days, as were pretreatment Glasgow Coma Scale score equal to or under 12 and Charlson Index scores of comorbidities of 3 or more. However, only the Glasgow Coma Scale and Charlson Index scores were found to be independent predictors of disability, and the same two measures were also independent predictors of unfavorable outcome, defined as high disability or mortality. Cerebrovascular disease plus anoxic ischemic and multiplex concomitant etiology, refractory SE and Glasgow Coma Scale score equal to or under 12 were predictors of mortality at three months. History of previous epilepsy was found to be a protective factor to survive an SE episode. Etiologies with structural cerebral lesions exhibited higher mortality rate than the other etiological groups. Our results, from Ecuador, a developing country, resemble those from more developed countries, from where most of the empirical clinical knowledge about SE has originated. Nevertheless, some differences were observed, such as higher mortality, lower prevalence of nonconvulsive SE, lack of association between patient age and either disability or mortality, and relatively long hospital stays in our sample compared to previous reports.

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Ethical approval

The execution and publication of this study was approved by the ethical committee of the institution.

Informed consent

Informed consent was obtained from all individual participants included in the study or their relatives.

Author contributions

1. DRR designed the study, collected and processed the data, performed the statistical analyses, completed the analysis of the results and wrote the manuscript.
2. GP wrote the final manuscript and performed statistical analyses.

Declaration of Competing Interest

The authors declare there are no conflicts of interest.

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