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ORIGINAL WORK

Predisposing Factors of Progression from Refractory Status Epilepticus to Super-Refractory Status Epilepticus in ICU-Admitted Patients: Multicenter Retrospective Cohort Study in a Resource-Limited Setting

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Abstract

Background: Super-refractory status epilepticus (SRSE) is an extremely serious neurological emergency. Risk factors and mechanisms involved in transition from refractory status epilepticus (RSE) to SRSE are insufficiently studied.

Methods: This was a multicenter retrospective cohort study of consecutive patients diagnosed and treated for RSE at two reference hospital over 5 years in Ecuador. A total of 140 patients were included. Potential demographic, clinical, and treatment variables that may predict progression from refractory to SRSE were analyzed.

Results: Super-refractory status epilepticus was identified in 67/140 (48%) of patients. In univariate analyses, level of consciousness on hospital admission (Glasgow Coma Score < 12, odds ratio [OR] 2.9, $p < 0.01$), traumatic brain injury (OR 2.3, $p = 0.05$), acute etiology (OR 3.0, $p = 0.04$), higher Status Epilepticus Severity Score (STESS) (OR 1.7, $p < 0.01$), and new clinical or electrographic seizure within 6 h (OR 4.2, $p < 0.01$) of starting anesthetic infusion were important factors related to super-refractory disease. The best independents predictors of SRSE when the presence of other potential factors were considered for multivariate analysis. Two models were calculated to avoid interactions between similar variables. Glasgow Coma Score on hospital admission < 12 (OR 3.1 [95% confidence interval {CI} 1.16–8.29], $p = 0.02$) and new clinical or electroencephalography (EEG) seizure after first 6 h of starting anesthetic infusion (OR 3.1 [95% CI 1.36–7.09], $p = 0.01$) were associated with higher risk of progression to SRSE in model 1. In contrast, model 2 indicated that patients with STESS ≥ 3 points (OR 2.9 [95% CI 1.24–6.65], $p = 0.01$) and new clinical or EEG seizure after 6 h starting anesthetic infusion (OR 3.0 [95% CI 1.32–6.97], $p = 0.01$) were the factors independently related to super-refractory disease.

Conclusions: The rate of patients with RSE admitted to intensive care units developing SRSE was high. Low level of consciousness on admission, higher STESS scores, and patients who did not achieve total control of clinical or EEG seizure in the first 6 h of starting intravenous anesthetic infusion may be early indicators of SRSE.

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Introduction

Status epilepticus (SE) is a neurological emergency in which seizures develop but mechanisms responsible for seizure termination fail or the initiation mechanisms drive to abnormally prolonged seizure (operational time 1), with long-term consequences if not controlled (operational point 2) [1].

Although in many cases these seizures can be controlled with antiseizure medications (ASMs), in some patients, SE persists despite the administration of at least two appropriately selected and dosed parenteral medications, including a benzodiazepine, which is known as refractory SE (RSE). However, in the most resistant cases, even this does not stop additional seizures from occurring. Super-refractory SE (SRSE) is defined as "SE that continues or recurs 24 h or more after the onset of anesthetic therapy, including those cases where SE recurs on the reduction or withdrawal of anesthesia" [2].

The term was introduced in 2011 at the Third London-Innsbruck Colloquium on SE [3]. Despite more than a decade passing since then, there is still very limited clinical evidence available concerning incidence, predisposing factors, pathophysiology, treatment, and outcome of SRSE.

This is a pressing clinical issue, as an estimated 10–15% of all patients admitted to hospital with SE progress to be classified as having SRSE [4–6]. For patients with RSE admitted to intensive care units (ICUs), an estimated 35–50% who require treatment with anesthetic drugs will meet criteria for SRSE [5–7]. However, the risk factors and mechanisms involved in progression from refractor to SRSE are poorly studied, and work on prediction of occurrence is scarce [4].

Inflammatory etiologies, such as encephalitis and other central nervous system (CNS) infections, have been identified as potential factors in the development of SRSE in patients who already have RSE [6, 7]. Lower premorbid modified Rankin Scale and nonconvulsive SE in coma have also been associated with risk of SRSE [4]. Nonetheless, several authors recognize that a knowledge gap for predicting SRSE exists, and thus there is an urgent need for clinical studies that can contribute to the evidence base [4, 7, 8]. Even within the limited available corpus of clinical data, varying definitions of SRSE, study settings, and patient samples are obstacles to understanding the demographic and clinical features associated with its occurrence. Early identification of patients at high risk for development of SRSE could help in clinical practice to identify the patients who require closer monitoring, and more aggressive and quick escalations of treatments. For these reasons, our aim was to evaluate the factors associated with the risk of progression from refractory to SRSE in patients admitted to ICUs. We hypothesized that factors related to severity, clinical characteristics of patients, etiology, aspects of treatment, and time to respond to them would be associated with progress from refractory to SRSE.

Methods

Settings

This is a retrospective multicenter cohort study that included variables of all consecutive patients with RSE hospitalized in the ICU from November 2015 to January 2020 at two major hospitals in Ecuador: Eugenio Espejo Hospital (Quito) and Luis Vernaza Hospital (Guayaquil). Both the Quito and Guayaquil research sites are large hospitals in urban areas. They are both health care and teaching centers associated with large state-run universities. Services include 24/7 emergency departments for around 3 and 5 million of people, with 414 and 640 hospitalization beds, respectively. Luis Vernaza Hospital is part of the charity board of Guayaquil city and is one of the largest nonprofit general health care centers in the country, with more than 21 thousand hospital admissions per year. It is located in the most populous city. Eugenio Espejo Hospital is a public hospital of Quito, the national capital, and receive more than 16 thousand hospital admissions per year.

Treatment Protocol

Patients were treated following the institutional protocols of the participating hospitals, which included the recommendations proposed by the Neurocritical Care Society [9, 10]. All patients received benzodiazepine (midazolam, diazepam) as first-line treatment and continued with second-line ASMs such as phenytoin, levetiracetam, valproic acid, lacosamide, in cases without seizure control [10].

Doses and administration route were applied according to international recommendations. The anesthetic drug (midazolam, propofol, thiopental, ketamine) was selected according to comorbidities, suspected etiology, clinical signs, and preference of the intensive care specialist. Midazolam and propofol were the most common

anesthetics drugs used as initial treatment in the ICU. Thiopental or ketamine were added in a few cases when midazolam or propofol were not practical for SE cessation, due to less accessibility in our limited context.

Continuous electroencephalography (EEG) monitoring was not performed because it was not available in the two centers conducting the study. Brief EEG studies (international 10–20 system) were performed in the first 2 h of the SE diagnosis, with 30–120-min durations of recording, and then repeated between 5 and 6 h after starting midazolam or propofol infusion in the ICUs. A daily brief EEG study (international 10–20 system, 30–120 min duration) was used to guide the minimum doses of anesthetics drugs needed to obtain a burst suppression pattern or avoid the patterns related with nonconvulsive SE (NCSE) and to confirm or exclude the diagnosis of psychogenic seizures. Doses of anesthetics drugs were only adjusted or retired during daily brief EEG monitoring [10]. EEG studies were interpretated by neurophysiology and neurologist specialists.

Study Design

Inclusion and Exclusion Criteria

The study inclusion criteria were age 16 years or older, diagnosis of RSE (defined as SE persisting despite administration of at least two appropriately selected and dosed parenteral ASMs, including a benzodiazepine [3, 5]), treated with continuous infusion of anesthetic drugs, and admitted to the ICU.

The exclusion criteria were nonavailability of the variables studied, incomplete hospital follow-up, and patients without SRSE progression confirmed.

In total, 148 patient charts were reviewed as potential cases; however, six were excluded from the study for not meeting inclusion or exclusion criteria (four because their SE was treated with benzodiazepine at subanesthetic dosing but did not require admission to the ICU, and two because their SE was handled with second-line ASMs), all at Eugenio Espejo Hospital. Two cases, at Luis Vernaza Hospital were excluded from analysis due to incomplete data and loss to follow-up (Fig. 1). Consequently, a total of 140 patients with RSE admitted to ICUs were included. Ninety-eight of the 140 patients with RSE (70%) were patients at Luis Vernaza Hospital, and the other 42 were patients at Eugenio Espejo Hospital.

The sample size was obtained from patients diagnosed and treated consecutively for RSE during the previously mentioned period. In this study, a sample size calculation was not performed.

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 institutional research ethics committees at the two research sites.

Definitions, Variables, and Outcome

Demographic information (e.g., age, sex) and history of seizures were recorded. SE classification was made: with prominent motor phenomena or without prominent motor phenomena (NCSE at onset), and the latter was defined using the Salzburg criteria [11].

Best consciousness level, grouped according to Glasgow Coma Score (GCS) on hospital admission, was recorded.

Etiology of SE was classified into groups: epilepsy, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or anoxic ischemic lesion, traumatic brain injury (TBI), systemic or metabolic (hyponatremia, uremic and hepatic encephalopathies, thyroid diseases, sepsis, shock, alcohol withdrawal, drugs or toxins, etc.), CNS infections, new-onset RSE [3], tumors (primary CNS or metastatic), or degenerative (Alzheimer disease, mitochondrial disease, Creutzfeldt-Jakob disease, congenital disorders, etc.), and autoimmune disorders (e.g., autoimmune encephalitis, multiple sclerosis, systemic lupus erythematosus, Sjogren disease, etc.).

Acute symptomatic etiology was designated if patients had SE with close temporal association to an acute CNS insult (7 days for cerebrovascular disease, TBI, anoxic encephalopathy, or intracranial surgery, active CNS infection, etc.; and 24-h for metabolic disturbances, toxic, sepsis, shock). If observed, focal structural lesion (lobar lesion or two continuous lobes in the same hemisphere) in neuroradiological studies was recorded. Status Epilepticus Severity Score (STESS) [12] was evaluated for all patients at hospital admission and was registered by a neurologist or intensivist who treated the patient. SRSE was defined as recurrence of SE 24 h or more after the start of anesthetic therapy, or when SE recurred on the reduction or withdrawal of anesthetics [2]. In addition, factors related to treatment were recorded, such as length of hospital and ICU stay, maximum doses and durations of midazolam or propofol infusions, whether vasopressors were needed during intravenous administration of anesthetic drugs, and severe hypotension requiring anesthetic dose reduction or withdrawal.

Withdrawal seizure was recorded if a seizure occurred within 48 h of completing the wean from anesthetic drugs. Tracheostomy and withdrawal of care were registered. Patients who were seizure-free after 24 h of anesthetic drug infusion were considered to have responded

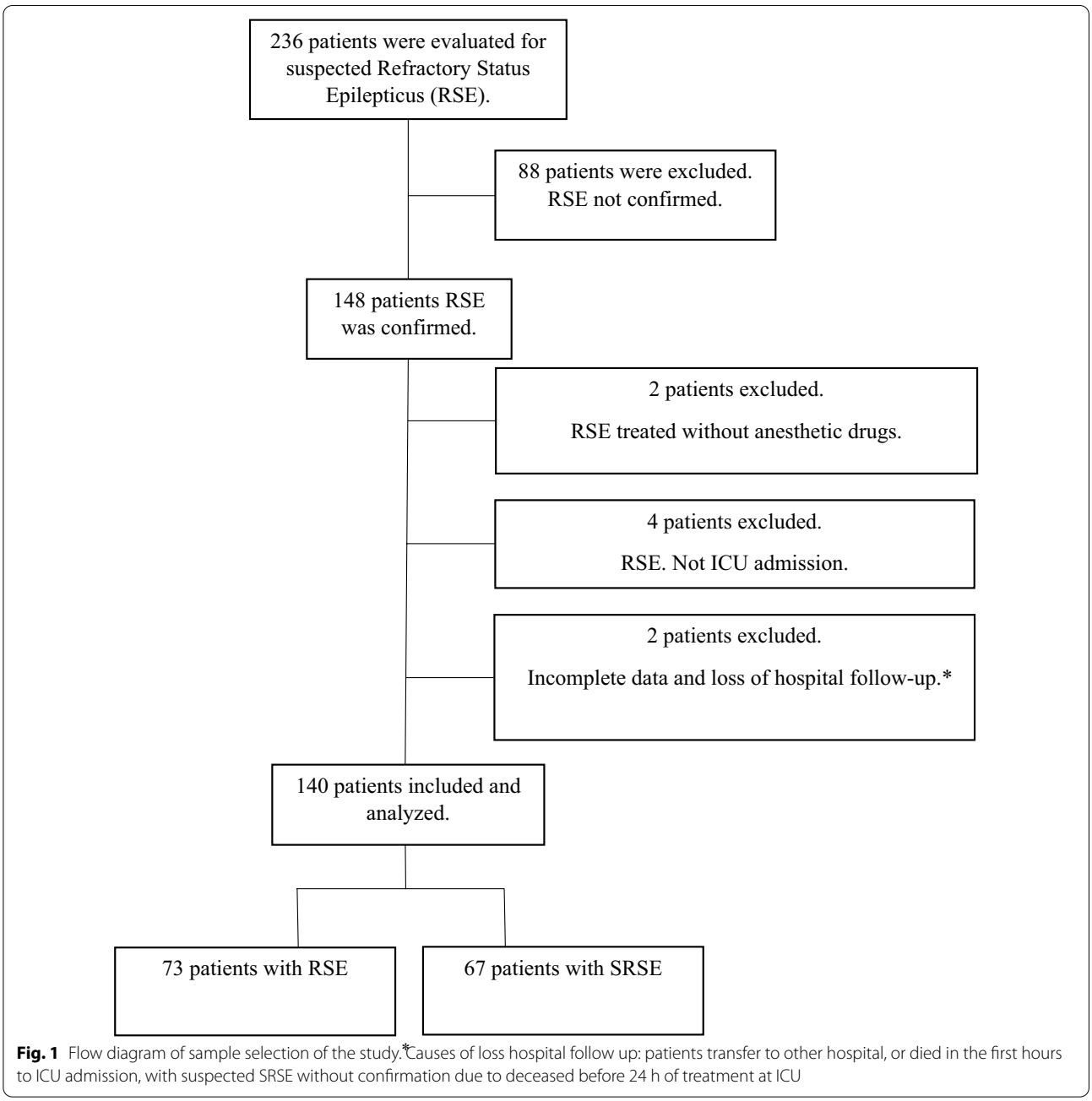

Fig. 1 Flow diagram of sample selection of the study. *Causes of loss hospital follow up: patients transfer to other hospital, or died in the first hours to ICU admission, with suspected SRSE without confirmation due to deceased before 24 h of treatment at ICU

to treatment (SE cessation). New clinical or electrographic seizure within the first 6 h of anesthetic infusion was also included in our analysis (electrographic seizure defined as rhythmic discharge or spike and pattern with definite evolution in at least two factors of morphology, frequency, or location, lasting at least 10 s). The selection of the initial 6 h was arbitrary, and the main reason was administrative; it is a time we usually can repeat brief EEG. The modified Rankin Scale [13] was used to evaluate outcome at hospital discharge.

Statistical Analysis

Data were summarized as means and standard deviations for continuous variables and as frequencies for categorical variables. Bootstrapping was used to calculate 95% confidence interval (CI) ranges. For initial analyses to identify factors associated with SRSE compared with RSE, continuous variables were analyzed with *t*-tests (two-tailed analyses), if the data set was normally distributed, based on analysis of skew and kurtosis, or with Mann–Whitney *U*-tests (effect sizes given as Cohen's

d). Categorical data were analyzed with χ^2 (with continuity corrections for 2×2 tables) or Fisher's exact test if expected cell counts were low (effect sizes given as Cramer's V).

Multivariable binary logistic regression modeling was used to identify independent factors predictive of SRSE occurrence (with effect sizes given as odds ratios with 95% CIs). A receiver operating characteristic curve was calculated for STESS to assess the accuracy to identify patients who would progress to SRSE. For tests of statistical significance, a *p* value threshold of 0.05 was employed. All statistical analyses were conducted with IBM SPSS 29.0.

Results

Prevalence and Course of Treatment of Patients with RSE Admitted to ICUs

In total, 140 patients, all with RSE and admitted to ICUs, were analyzed. The mean age of patients was 41 years (range 16–84 years), with a male predominance at 63% (88/140). Nearly one quarter (24%, 34/140) of patients had preexisting seizure history. The median STESS was 3 (range 0–5). On presentation at the hospital, the most common type of SE was with prominent motor phenomena, displayed by nearly half of the cohort (56%, 79/140), the most common etiology was TBI (30%, 42/140), and the majority of cases (62%, 87/140) had a GCS < 12. New clinically or EEG-observed seizures occurring within the first 6 h of anesthetic infusion were noted in 57% (80/140) of patients, whereas withdrawal seizures occurred in 31% (44/140) of patients. Of the 140 admissions for RSE, 67/140 (48%) were classified as SRSE when responses to ICU treatment were considered. Data for treatment factors and course are summarized in Table 1 for all patients ($N=140$), as well as comparison by those patients who had only RSE ($n=73$) and those who were found to have SRSE ($n=67$). As would be expected, ICUs stay was significantly longer in patients with SRSE compared with patients with RSE by about 8 days. Overall, hospital mortality was high at 46% (64/140).

Regarding anesthetics applied, midazolam was more often used than propofol and was more often used as a first-line treatment. However, there were no significant differences between RSE and SRSE cases in maximum dose used or duration of treatment. In contrast, propofol was employed for significantly longer, and at higher doses, in patients with SRSE compared with those with RSE.

Patients with SRSE, compared with RSE, were significantly more likely to have a new seizure (clinical or electrographic) within the first 6 h of anesthetic administration (odds ratio 4.2, 95% CI 2.05–8.67) and to suffer anesthetic withdrawal seizures (odds ratio 2.56, 95% CI 1.22–5.35), as expected, taking into account that it is a criterion for defining SRSE. They were also significantly more likely to require tracheostomy (odds ratio 2.60, 95% CI 1.29–5.24).

Hospital outcome was significantly worse for patients treated as SRSE, who, more likely than not, had an unfavorable outcome, that is, Rankin score 5 or 6 (observed range of outcome scores was 1–6), compared with patients with only RSE, who were more likely than not to have a favorable outcome, that is, Rankin scores 1–4 (observed range of outcome scores 0–6).

Clinical Presentations of Patients with RSE and Factors Related to SRSE

Several statistically significant factors associated with progress to SRSE were identified via univariate analyses: Consciousness level on hospital admission was significantly associated ($p<0.01$), with a modest effect size. Alert patients (GCS 15–14) were less likely to (odds ratio 0.26, 95% CI 0.11–0.63) and stuporous/comatose (GCS < 12) patients were more likely to (odds ratio 2.86, 95% CI 1.4–5.9) progress to SRSE.

As would be expected, STESS scores on presentation were significantly higher in patients who later progressed to SRSE, $p<0.01$, Nagelkerke $R^2=0.09$, with a β value of 1.65 (95% CI 1.18–2.30), indicating an estimated 65% increase in risk of SRSE associated with each point increase on the STESS score.

Patients with acute etiology were significantly more likely to manifest SRSE compared with those with nonacute etiology (odds ratio 3.04, 95% CI 1.18–8.25). Etiology type significantly related with progression to SRSE. Compared with other presenting etiologies, patients with systemic/metabolic disorder were significantly less likely to manifest SRSE (odds ratio 0.22, 95% CI 0.06–0.80), and with a statistically moderate effect size. There was a smaller effect size, and in contrast, acting as a positive risk factor, for patients with TBI to have SRSE (odds ratio 2.26, 95% CI 1.08–4.74).

Regarding etiologies, it is also of clinical interest to consider which are more associated with SRSE compared with epilepsy.

To identify the best set of presenting variables that independently predict progression to SRSE, we selected candidates from Table 1 that were either significant predictors, or might be when included in multivariable models, and were independent measurements (Table 2). The etiologies were grouped for analysis, and the center involved in patient care was introduced to assess differences in protocol treatment between hospitals and their impact on results. STESS was not included in model 1 because the scores are dependent on some of the other variables included. This analysis, with all five variables

Table 1 Demographic and clinical characteristics of patients admitted to ICUs, and comparison of factors between those with refractory and super refractory status epilepticus

	All cases[a] *N* = 140	95%CI	RSE[a] *n* = 73	SRSE[a] *n* = 67	Sig	Effect size (*d*/*V*)
Demographics						
Age	41.2 (19.6)	38.9–48.9	42.6 (20.0)	39.6 (19.2)	.37	.15[d]
Sex (male)	88 (63%)	55–71%	46 (63%)	42 (63%)	> .99	< .01[V]
Clinical features and history						
Seizure history	34 (24%)	17–31%	22 (30%)	12 (18%)	.14	.14[V]
Classification of SE at onset					.23	.11[V]
With prominent motor phenomena	79 (56%)	47–64%	45 (61%)	34 (51%)	.34	.08[V]
Wtihout prominent motor phenomena	61 (43%)	35–53%	28 (39%)	33 (49%)	.18	.12[V]
Consciousness level on hospital admission					< .01	.28[V]
Glasgow Coma score (GCS) 15–14	33 (24%)	17–31%	25 (34%)	8 (12%)	< .01	.26[V]
Glasgow Coma score (GCS) 13–12	20 (14%)	9–21%	11 (15%)	9 (13%)	.97	.02[V]
Glasgow Coma score (GCS) < 12	87 (62%)	53–70%	37 (51%)	50 (75%)	< .01	.25[V]
Etiology SE					.04	.38[V]
Epilepsy	22 (16%)	10–22%	13 (18%)	9 (13%)	.63	.06[V]
Ischemic stroke	10 (7%)	3–11%	4 (5%)	6 (9%)	.56	.09[V]
Intracerebral hemorrhage	6 (4%)	1–8%	5 (7%)	1 (1%)	.22	.15[V]
Subarachnoid hemorrhage	6 (4%)	1–8%	4 (5%)	2 (3%)	.75	.09[V]
Traumatic brain injury	42 (30%)	23–38%	16 (22%)	26 (39%)	.05	.18[V]
Systemic/metabolic	18 (13%)	8–18%	14 (19%)	4 (6%)	.03	.21[V]
CNS infections	20 (14%)	9–20%	9 (12%)	11 (16%)	.65	.10[V]
Primary brain tumors and brain metastases	2 (2%)	0–3%	2 (3%)	0	–	–
Degenerative diseases	3 (2%)	0–5%	3 (4%)	0	–	–
NORSE	3 (2%)	0–5%	1 (1%)	2 (3%)	.42	.07[V]
Autoimmune diseases	7 (5%)	1–9%	2 (3%)	5 (8%)	.36	.13[V]
Anoxic	1(1%)	0–2%	0	1(1%)	–	–
Acute etiology	116 (84%)	77–89%	56 (77%)	60 (91%)	.04	.19[V]
Focal structural lesion in neuro-radiological studies	73 (52%)	44–60%	33 (45%)	40 (60%)	.12	.15[V]
STESS score	2.6 (1.1)	2.4–2.8	2.3 (1.1)	2.9 (1.0)	< .01	.57[d]
Treatment and outcome						
Hospital stay in days	41.8(29.0)	37.1–46.8	38.8(28.6)	44.9 (29.3)	.22	.30[d]
ICU stay in days	25.2(20.6)	21.7–28.6	21.3(19.2)	29.4 (21.4)	< .01	.40[d]
Midazolam max/dose (mg/Kg/h)[b]	0.35 0.22	0.31–0.39	0.36(0.24)	0.34 (0.20)	.94	.09[d]
Midazolam treatment (days)[b]	6.3 (5.4)	5.4–7.2	6.5 (5.3)	6.1 (5.5)	.87	.08[d]
Propofol max/dose (mcg/Kg/min)[c]	82.0 (49.2)	72.4–92.7	63.1(40.1)	87.1 (50.3)	.06	.53[d]
Propofol treatment (days)[c]	3.7 (2.0)	3.4–4.2	2.8 (1.4)	4.0 (2.1)	.04	.68[d]
New clinical or EEG seizure after first 6 h starting anesthetic infusion	80 (57%)	49–65%	30 (41%)	50 (75%)	< .01	.34[V]
Withdrawal seizures	44 (31%)	24–39%	16 (22%)	28 (42%)	.02	.21[V]
Vasopressors administered	75 (54%)	45–62%	34 (47%)	41 (61%)	.12	.15[V]
Severe hypotension	63 (45%)	37–54%	27(37%)	36(57%)	.07	.17[V]
Tracheostomy	84 (60%)	52–68%	36(49%)	48(72%)	.01	.23[V]
Withdrawal of care	9 (6%)	3–11%	3 (4%)	6 (9%)	.21	.10[V]
Hospital outcome (Rankin scale)	4.2 (2.0)	3.9–4.5	3.8 (2.1)	4.7 (1.7)	< .01	.47[d]
Rankin 0–2	33 (24%)	20–32%	25(34%)	8(12%)	.01	.38[V]
3–4	35 (25%)	22–32%	17(23%)	18(27%)	.16	.07[V]
5–6	72 (51%)	43–63%	31(43%)	41(61%)	.03	.27[V]
Hospital mortality	64 (46%)	37–54%	29(39%)	35(52%)	.17	.19[V]

Table 1 (continued)

[a] Column summaries are mean (± SD) for continuous variables and count (%) for categorical variables; [b]Midazolam was used as first line anesthetic medication in 91 cases, after other anesthetic medication in 27 cases, and not was administered in 22 cases. Dosage and days of treatment was calculated on all cases that received it ($n = 118$). [c]Propofol was used as first line anesthetic medication in 42 cases, after other anesthetic medication in 43 cases, and not was administered in 55 cases. Dosage and days of treatment was calculated on all cases that received it ($n = 85$)

RSE, refractory status epilepticus; SRSE, super refractory status epilepticus; EEG seizure, electrographic seizure; withdrawal seizures, seizures occurring within 48 h of completing the anesthetic drugs wean; severe hypotension, hypotension requiring decreased doses of IV anesthetics drugs; NORSE, new onset refractory status epilepticus. SE, Status epilepticus. STESS score, Status Epilepticus Severity Score; 95% CI 95% confidence interval of the mean or the count percentage of the full sample ($N = 140$); Sig., significance of the difference between RSE and SRSE groups. Effect size = Cohen's d for continuous variables and Cramer's V for categorical variables

entered together as covariates, produced a significant model predicting progression from RSE to SRSE, with a Nagelkerke R^2 of 0.26, $p < 0.01$.

GCS on hospital admission < 12, odds ratio 3.1 (95% CI 1.16–8.29), $p = 0.02$, and new clinical or EEG seizure after the first 6 h starting anesthetic infusion (odds ratio 3.1 [95% CI 1.36–7.09], $p = 0.01$) were independently associated with progression from RSE to SRSE within that model.

When the analyses were performed with STESS and excluded GCS at hospital admission (model 2), we found similar results. STESS ≥ 3, odds ratio 2.9 (95% CI 1.24–6.65), $p = 0.02$, and new clinical or EEG seizure after the first 6 h starting anesthetic infusion (odds ratio 3.0 [95% CI 1.32–6.99], $p = 0.01$) were the factors related to progression to SRSE, with Nagelkerke R^2 of 0.27, $p < 0.01$ (Table 2).

Because STESS was a good predictor of progression to SRSE in previous analyses, we decided to calculate the receiver operating characteristic curve and determine its optimal cutoff point (Fig. 2).

The area under curve was 0.64 (95% CI 0.54–0.73), $p = 0.01$. Values ≥ 3 points in STESS showed a sensitivity of 66% and a specificity around 58% to identify patients with SRSE. Table 3 shows the sensitivity and specificity values according STESS scores, and the univariate analyzed STESS dichotomized under 3 points, versus equal to or more than 3 points, $p < 0.01$, Nagelkerke $R^2 = 0.60$, with an odds ratio of 2.6 (95% CI 1.30–5.14).

Discussion

The aim of this multicenter cohort study was to evaluate the predisposing factors associated with progression of RSE diagnosis to SRSE. Given this substantial heterogeneity of presentations, identifying risk factors for SE that is super refractory is challenging. Nevertheless, the current study reports on a relatively large sample of what is a rather rare clinical condition.

Despite the rarity of cases of RSE, treatment resistance sufficient to diagnose super refractoriness was very common within this cohort of patients admitted to ICUs for the refractory nature of their SE. In fact, almost half of all cases (48%) were classified as super refractory. As would be expected, those patients had worse prognoses. They had significantly longer ICUs stays, worse outcomes indicating greater disability as measured on the modified Rankin Scale at hospital discharge, and they were significantly were more likely to require tracheostomy. Similar results were found in a French cohort, and a study at an Indian center, with 40% and 41% of ICU admitted patients with RSE progressing to SRSE, respectively [6, 7]. Unfortunately, limited data are available, but according to these results, and our data, a substantial proportion of ICU patients with RSE develop SRSE.

The main findings on risks for lack of response to treatment identified several clinical factors related to progression to SRSE. State of consciousness on admission was a statistically significant predictor of SRSE, with worse prognosis for those patients who were not alert. In fact, even with etiological factors held constant, state of consciousness remained an independent (GCS < 12) predictor of extreme treatment resistance (i.e., progression to SRSE). A German cohort study published in 2017 indicated NCSE in coma as an independent predictor of SRSE [4], but did not find associations between level of consciousness (stuporous or comatose) at hospital admission. The author suspected that in our context brief EEG monitoring is insufficient to identify all potential patients with NCSE in coma and would be an explanation for this difference.

It is also of note in our sample, that occurrence of new clinical or EEG seizures within 6 h of commencing anesthetic infusion was related to risk of developing into super-refractory disease. In other words, patients with uncontrolled clinical or electrographic seizures in the first hours of starting anesthetic therapy were 3.2 times more likely to continue that clinical or EEG pattern at 24 h, or to suffer withdrawal seizure (i.e., be reclassified as SRSE). The authors suspect that this finding might be related to the refractoriness of the SE itself, or to insufficient treatment.

In our series, EEG seizure was treated in all patients with bolus of benzodiazepine or propofol, and increased doses of anesthetic infusion. The objective of this approach is to attempt to completely suppress all EEG patterns related to EEG seizures, and/or NCSE. Strong evidence to support aggressive treatment for patients with frequent electrographic seizures such as NCSE is lacking. However, some clinical studies have

Table 2 Multivariate analysis of factors related with progression to from refractor to super refractory status epilepticus

	Odds ratio	95%CI of OR	Sig
Variables (Model 1)			
Glasgow coma score on hospital admission < 12	3.1	1.16–8.29	.02*
Etiology groups SE$^{\Omega}$			
Cerebrovascular disease	1.6	0.29–8.61	.59
Traumatic Brain Injury	0.9	0.23–3.57	.89
Systemic/metabolic	1.5	0.43–5.34	.53
CNS infections	0.3	0.06–1.66	.17
Others etiologies	1.2	0.31–5.21	.74
Acute etiology SE	2.2	0.46–10.52	.32
New clinical or EEG seizure after first 6 h starting anesthetic infusion	3.1	1.36–7.09	.01*
Center involved in the patient's care	0.9	0.31–2.46	.80
Variables (Model 2)			
STESS ≥ 3	2.9	1.24–6.65	.01*
Etiology groups SE$^{\Omega}$			
Cerebrovascular disease	2.1	0.37–12.05	.41
Traumatic Brain Injury	0.6	0.15–2.54	.51
Systemic/metabolic	1.8	0.49–6.47	.39
CNS infections	0.3	0.05–1.52	.14
Others etiologies	1.2	0.29–5.02	.79
Acute etiology SE	2.5	0.51–11.92	.26
New clinical or EEG seizure after first 6 h starting anesthetic infusion	3.0	1.32–6.97	.01*
Center involved in the patient's care	0.9	0.36–2.51	.91

Model 1. Excluded STESS due to the score contained consciousness level items

Model 2. Excluded Glasgow Coma score to avoid interactions with STESS (consciousness level items)

Center involved in patient care: Luis Vernaza Hospital—Eugenio Espejo Hospital

Cerebrovascular disease included: Ischemic stroke, Intracerebral hemorrhage, Subarachnoid hemorrhage

Others etiologies grouped: Degenerative disease, new onset refractory status epilepticus, autoimmune, anoxic, primary brain tumors and brain metastases

CI: confidence interval. CNS: central nervous system. EEG: electroencephalogram. OR: Odds ratio

$^{\Omega}$ Epilepsy as reference. *$p \leq 0.05$

demonstrated that the total amount of time spent in ictal activity (seizure burden) while in the ICU is associated with unfavorable outcome [14–16].

On the other hand, intensive treatment to obtain a cessation of suspicious EEG activity of NCSE and electrographic seizures can lead to oversedation. In contrast, underestimation of the risk of EEG activity such as lateralized periodic discharges, especially lateralized periodic discharges plus (i.e., > 2 Hz and/or with rhythmic or fast activity), and attributing the EEG pattern only to structural brain lesions could drive a secondary cerebral injury, with consequent impairment of patients [17]. This is the reason why continuous EEG monitoring is a cornerstone of the evaluation of patients with SE admitted to ICUs. Intermittent EEG monitoring is insufficient to avoid overtreatment or insufficient treatment of RSE. Unfortunately, this may not always be available, particularly in highly resource-limited contexts [18], such as many state-funded hospitals in low and middle-income countries.

Our initial comparison of refractory to SRSE cases also confirmed that etiological factors were particularly important. Patients with TBI, and acute symptomatic etiology were more likely, compared to the other causes, to have SE that was anesthetic treatment–resistant, and be subsequently diagnosed as super refractory. However, the binary logistic regressions analyzed were somewhat underpowered due to excluding all patients bar those with epilepsy or the target etiology. Consequently, no significant associations could be confirmed, and the confidence intervals of the odds ratios were very wide. Encephalitis/CNS infections have previously been associated with progression from refractory to SRSE [4, 6, 7]. However, we observed no such associations in the current study. This may partly be due to the low prevalence of such infections within our sample, and consequent low statistical power to detect associations. In total only 20 patients appeared to have RSE due to CNS infections, and although more often than not they progressed to

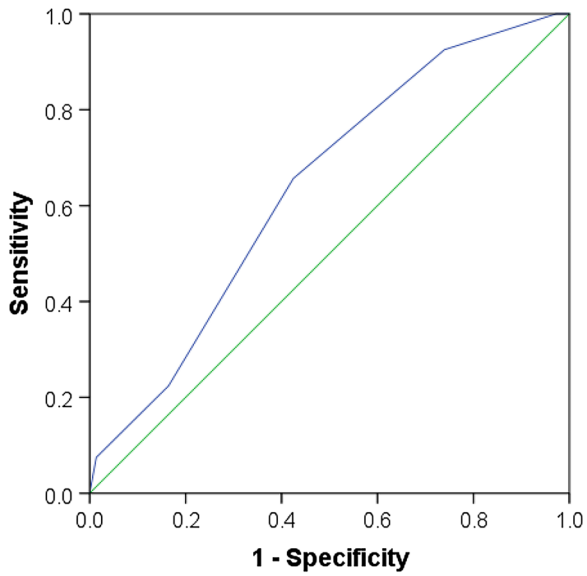

Fig. 2 Receiver operating characteristic curve (ROC) of Status Epilepticus Severity Score for identified patients with Refractory Status Epilepticus to progress to Super Refractory Status Epilepticus

being classified as super refractory, the effect was not statistically significant.

It has previously been recognized that SE etiologies following acute brain injury such as infection, trauma, or stroke are more expected to produce seizures that are refractory, compared to epilepsy or remote symptomatic causes [3, 19].

Some authors consider that the progression to SRSE is not only due to the primary cerebral mechanism of injury, as ensuing molecular and cellular processes likely play a role [4, 5]. As a consequence of underlying pathology and/or the effects of SE, the brain may become intrinsically unstable in the post-ictal state. Some of the proposed mechanisms that may lead to further cerebral damage and prolongation of seizures are inflammation, breakdown of the blood–brain barrier, altered network connectivity, altered receptor/ion channel expression, and altered neurotransmitter release [20].

Other results exposed in our series was the modest accuracy of STESS score (area under the curve 0.64, 95% CI 0.55–0.73) to identified SRSE among patients admitted to ICUs for refractory disease. Though, a regression analysis suggested that the only independent factor contributing to STESS scores success in prediction of SRSE was (impaired) consciousness level. The authors believe that it could be a cost-free clinical tool that would aid in treatment decisions for these patients. There is substantial potential for future research that explorers the accuracy of different severity scores tools , to predict SRSE. In addition to STESS this could include EMSE (Epidemiology-based Mortality score in Status Epilepticus), and END-IT (Encephalitis, NCSE, Diazepam resistance, Image abnormalities and Tracheal intubation) methods.

A limitation of this study is its observational design with all the biases that influence such studies, nevertheless the analysis of illness progression over time, including ICU stay length and mortality allow for some prospective interpretation. The unavailability of continuous EEG monitoring in our study centers could have reduced the clinical teams' ability to identify NCSE patterns, and consequently delayed aggressive anesthetic infusion, increasing rates of super-resistant cases of SE. Thus, our data may not mirror patient profiles in other health care contexts that have access to continuous EEG. Conversely, in some cases, maintaining high dose anesthetic treatment may have caused overtreatment until the next EEG study, with subsequent complications that could have prolonged ICU hospitalization. However, availability of 24 h EEG monitoring does not appear to be

Table 3 Evaluation of the diagnostic performance of different STESS scores and the dichotomized analysis of the scale for predicting the progression from RSE to SRSE

STESS score	RSE $n=73$	SRSE $n=67$	Total patients $n=140$	Sensitivity	Specificity
0–1 points	19 (14%)	5 (3%)	24 (17%)		
2 points	23 (16%)	18 (13%)	41 (29%)	.92	.26
3 points	19 (14%)	29 (21%)	48 (35%)	.66	.58
4 points	11 (8%)	10 (7%)	21 (15%)	.22	.84
5 points	1 (1%)	5 (3%)	6 (4%)	.07	.98
Dichotomized STESS*	**$n=73$**	**$n=67$**	**$n=140$**	**Fisher's $T=.01$**	
STESS < 3 points	42 (30%)	23 (16%)	65 (46%)		
STESS ≥ 3 points	31 (22%)	44 (32%)	75 (54%)		

*Odds ratio = 2.6 (95%CI = 1.30, 5.14), $p < .01$

widely available even in hospitals in high-income countries [18].

Ideally, we would have analyzed latency to initial treatment of SE. The lack of a standardized prehospital treatment protocol, unwitnessed seizures, or late identification of subtle seizures in patients with diminished level of consciousness are some of the practical barriers to reliable recording of treatment latency time.

Evidence supports initiation of treatment as soon as possible for generalized convulsive SE (GCSE). The benefits of early clinical intervention include limited refractoriness, morbidity and mortality. The SENSE (Sustained Effort Network for treatment of Status Epilepticus) study found shorter latency from SE onset to commencement of treatment with benzodiazepines independently predicted a shorter time to SE cessation [21].

Less than half of patients with GCSE received benzodiazepine administration in the first 30 min in the SENSE study. In contrast, the average latencies to treatment in established SE were 60 min and 73 min in ESETT (Established Status Epileptics Treatment Trial) and ConSEPT (Convulsive Status Epilepticus Pediatric Trial) studies respectively [21–23].

We suspect substantially longer latencies to initial treatment in many middle-income countries, as a consequence of their generally resource-limited health care systems. One review has compared GCSE studies from around the world. They found that delays to first-line treatment of > 60 min were common in low and middle-income countries (67%), but relatively infrequent in high-income countries (21%) [24].

Unfortunately, data about prehospital or hospital commencement of treatment latency of our patients were not available for our cohort. Implementation of a standard protocol for early treatment, with transitional ASMs, starting with benzodiazepines, and aggressive treatment in patients with RSE could be made mandatory. This could be a first step to reduce morbidity and mortality of SE and diminish the rate of cases that progress to refractory or super-refractory levels.

Conclusions

The rate of patients with RSE admitted to ICUs who were found to have super-refractory disease was high. The most common etiology found in patients with RSE was TBI, and patients with TBI were also more likely to display SRSE than patients with cases of other etiologies. Patients with low levels of consciousness on admission and higher STESS scores and who did not achieve total control of clinical or EEG seizure in the first 6 h of starting intravenous anesthetic infusion also exhibited a higher risk of SRSE in our series of Ecuadorian patients, even despite the limitations that may be associated with the brief duration of EEG monitoring.

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Author Contributions
DRR: conceptualization of the study, data collection, review of the literature, data curation and analysis, manuscript preparation. TF project management, data collection and manuscript preparation. DDS and NM: study conceptualization, project management and manuscript preparation. YPS and MIM, literature review, interpretation of data, and manuscript preparation. GP data processing, analysis and interpretation, manuscript preparation. The final manuscript was approved by all authors.

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Conflict of interest
None.

Ethical Approval/Informed Consent
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