








FULL-LENGTH ORIGINAL RESEARCH

Factors associated with long-term outcomes in pediatric refractory status epilepticus

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Abstract

Objective: This study was undertaken to describe long-term clinical and developmental outcomes in pediatric refractory status epilepticus (RSE) and identify factors associated with new neurological deficits after RSE.

Methods: We performed retrospective analyses of prospectively collected observational data from June 2011 to March 2020 on pediatric patients with RSE. We analyzed clinical outcomes from at least 30 days after RSE and, in a subanalysis, we assessed developmental outcomes and evaluated risk factors in previously normally developed patients.

Results: Follow-up data on outcomes were available in 276 patients (56.5% males). The median (interquartile range [IQR]) follow-up duration was 1.6 (.9–2.7) years. The in-hospital mortality rate was 4% (16/403 patients), and 15 (5.4%) patients had died after hospital discharge. One hundred sixty-six (62.9%) patients had subsequent unprovoked seizures, and 44 (16.9%) patients had a repeated RSE episode. Among 116 patients with normal development before RSE, 42 of 107 (39.3%) patients with available data had new neurological deficits (cognitive, behavioral, or motor). Patients with new deficits had longer median (IQR) electroclinical RSE duration than patients without new deficits (10.3 [2.1–134.5] h vs. 4 [1.6–16] h, $p = .011$, adjusted odds ratio = 1.003, 95% confidence interval = 1.0008–1.0069, $p = .027$). The proportion of patients with an unfavorable functional outcome (Glasgow Outcome Scale-Extended score ≥ 4) was 22 of 90 (24.4%), and they were more likely to have received a continuous infusion.

Significance: About one third of patients without prior epilepsy developed recurrent unprovoked seizures after the RSE episode. In previously normally developing patients, 39% presented with new deficits during follow-up, with longer electroclinical RSE duration as a predictor.

KEY WORDS

clinical neurology, epilepsy, outcome research, pediatric, status epilepticus

1 | INTRODUCTION

Neurological sequelae of pediatric status epilepticus (SE) occur in 9%–28% of patients.^{1,2} Outcomes may be affected by additional clinical factors, including age at onset, etiology, SE duration,^{3–6} and time to treatment.⁷ Of those, SE duration and time to treatment are of particular importance, as they are potentially modifiable. SE is one of the most common neurological emergencies during childhood, with an overall estimated incidence of 18/100,000 children per year.^{6,8} Refractory convulsive SE (RSE) occurs in one third of patients with SE,^{9,10} and neurological sequelae—subsequent epilepsy; recurrent SE; behavioral, cognitive, or motor disabilities—may have a lifelong impact on patients.^{4,7,11,12} Additionally, pediatric SE is related to a 3% short-term mortality,^{2,6,13,14} which increases to 4%–4.7% in RSE,^{15,16} and up to 22% in the long term.^{13,17–20} RSE etiology is the main predictor for long-term morbidity.^{7,11} To date, limited information is available regarding the effect of potentially adjustable predictors, such as RSE duration or time to treatment, on RSE long-term outcomes.

We addressed this gap in knowledge by describing the long-term outcomes and analyzing factors associated with new neurological deficits and functional outcomes after pediatric RSE, including potentially modifiable risk factors, such as RSE duration. We hypothesized that the pediatric RSE duration may affect developmental outcomes, independent of etiology.

2 | MATERIALS AND METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review board at each participating institution. Written informed consent was obtained from the parents or guardians of each patient.

2.2 | Study design

We provide a retrospective analysis of prospectively collected data performed at 16 pediatric tertiary or quaternary hospitals within the Pediatric Status Epilepticus Research Group (pSERG).²¹ This consortium has collected data on children with SE since 2011 and assesses variability of care to delineate strategies for improving management and prognosis in pediatric RSE.²¹

2.3 | Patients

Inclusion criteria were (1) age = 1 month to 21 years; (2) admission to a pSERG institution between June 1, 2011 and

Key Points

- Long-term mortality rate after RSE was 5.4%, most commonly in the context of an underlying medical condition
- Half of the patients with no prior epilepsy developed recurrent unprovoked seizures, and 16.9% presented repeated RSE episodes during follow-up
- Almost 40% of patients with RSE had new neurological deficits at follow-up, and it was correlated with a longer electroclinical RSE duration
- An unfavorable GOS-E score (≥ 4) was independently associated with receiving at least one continuous infusion

March 8, 2020, with any cause of RSE; (3) focal or generalized convulsive seizures at the onset that continued after administration of at least two antiseizure medications (ASMs), including at least one nonbenzodiazepine ASM or the use of a continuous infusion to treat SE; and (4) any follow-up information available from at least 30 days after the RSE event to last follow-up visit. Exclusion criteria were (1) nonconvulsive SE detected on electroencephalogram (EEG) lacking convulsive seizure at onset, (2) death during the initial RSE hospital admission, and (3) lack of initial basic demographic and clinical data or follow-up data. If a patient presented with more than one RSE episode during the study period, only the first episode was included.

We collected data with a standardized data acquisition tool and entered cases into an electronic database. We obtained follow-up information for a minimum of 30 days after RSE onset through chart review. Initially, we analyzed clinical outcomes in all patients with RSE meeting inclusion criteria. Subsequently, we focused on a subgroup of developmentally normal patients—with or without prior epilepsy—before the sentinel RSE episode, and in whom changes in developmental outcome following RSE could, therefore, be determined from our clinical assessment-based approach. The development of patients before the RSE episode was evaluated clinically by chart review of the sentinel hospital admission and prior outpatient visits when available.

2.4 | Aims and variables

Our first aim was to describe clinical outcomes during follow-up in the entire RSE population. Our primary outcome for this first aim was the mortality after hospital discharge and at least 30 days following RSE onset. We reported the in-hospital mortality rate but excluded these patients from our final population, as they were out of our study focus.

Secondary outcomes were the development of new unprovoked seizures, use of ASMs or rescue medication, RSE recurrence, and newly discovered etiologies at follow-up.

Additionally, we investigated developmental outcomes in a subgroup of patients with normal development before the sentinel RSE episode. Our primary outcome for this second aim was the presence of any new neurological deficit (motor, cognitive, or behavioral) assessed as a dichotomous variable (yes/no). This was determined by the treating pediatric neurologist through clinical neurological assessment and documented in the patient's medical records at follow-up visits. Our secondary outcome was the Pediatric Glasgow Outcome Scale-Extended (GOS-E), a validated 8-point scale that evaluates functional outcome, ranging from upper good recovery to death (Figure S1).²² The score was calculated based on information from a retrospective chart review. Subjects were divided into two outcome groups: favorable outcome (GOS-E score < 4) and unfavorable outcome (GOS-E score \geq 4).²⁰

Furthermore, we evaluated the association of potential risk factors during the RSE event that predicted new neurological deficits and unfavorable functional outcomes. We considered electroclinical RSE duration (continuous; hours), etiology (structural/unknown/others), use of continuous infusions, history of epilepsy, sex, and age. The structural etiology was selected as the reference category for etiology, as it has been associated with worse outcomes.^{2,9,17,23} The electroclinical RSE duration was defined as the time from RSE onset to seizure cessation, either clinically or electrographically, as assessed by EEG monitoring, which was initiated as indicated by the treating physician. In the analysis of our secondary aim, the electroclinical RSE duration was the main predictor, controlling for the use of continuous infusions, etiology, history of epilepsy, sex, and age. In a subanalysis, we evaluated the presence of new neurological deficits with convulsive RSE duration as the main predictor, aiming to assess the effect of the convulsive RSE duration alone on the development of neurological deficits. Additionally, we assessed the association of the time to first benzodiazepine (BZD) and the development of neurological deficits through electroclinical RSE duration as a mediator variable. We described clinical variables such as RSE type defined as intermittent when the patient presented with multiple seizures and did not return to baseline, and continuous when the patient presented with an ongoing seizure.

2.5 | Statistical analysis

We used descriptive statistics to analyze demographic and clinical characteristics. We reported categorical variables with proportions (*n*) and percentages and continuous variables with median and interquartile range (IQR). We performed univariate analyses of categorical variables with Fisher exact test and quantitative variables with the Wilcoxon rank sum test. A

multivariate logistic regression model evaluated the effect of predictors on outcomes. We selected predictors and potential confounders based on prior medical knowledge. Causal mediation analysis was conducted as a post hoc analysis (Appendix S1). The two-sided α -value was set at .05. All statistical analyses were performed with R version 3.6.2,²⁴ RStudio,²⁵ and the packages *gdata*,²⁶ *car*,²⁷ *lubridate*,²⁸ *gmodels*,²⁹ and *mediation*.³⁰

3 | RESULTS

3.1 | Study population

We reported clinical outcomes in 276 patients with RSE with convulsive onset, and developmental assessment on a subpopulation of 116 patients with prior normal development (Figure 1). We followed the entire population for a median (interquartile range [IQR]) of 1.6 (.9–2.7) years (range = 31 days to 6.9 years; Figure 2). The median (IQR) follow-up period of the subgroup of patients with normal development before RSE was 1.8 (.9–2.7) years. Table 1 summarizes the demographics and clinical features.

3.2 | Aim 1: Clinical outcomes in the entire RSE population

3.2.1 | Mortality

Sixteen of 403 (4%) patients with a first episode of RSE in our initial cohort died during the hospital admission and were excluded (Figure 1). Fifteen of 276 (5.4%) patients had died after discharge and during the follow-up period. Therefore, 31 patients died during the study period, indicating a 7.7% overall mortality rate among the initial RSE cohort of 403 children. The median (IQR) follow-up period in those who died during follow-up was 7.6 (4.7–25.4) months. Table 2 summarizes characteristics of patients who died during outpatient follow-up. Ten (66.6%) patients died from complications of underlying medical conditions, including metabolic disorders in five (50%), and two (13.3%) patients died from sudden unexpected death in epilepsy: one without neurological history before the RSE event, and the other with a history of epilepsy and developmental delay, but no prior RSE. Both patients were on multiple ASMs after the sentinel RSE event and both had ongoing seizures and required further rescue medications during follow-up.

3.2.2 | New unprovoked seizures and prior epilepsy

At follow-up, 166 of 264 (62.9%) patients with available follow-up data on subsequent seizures continued to have

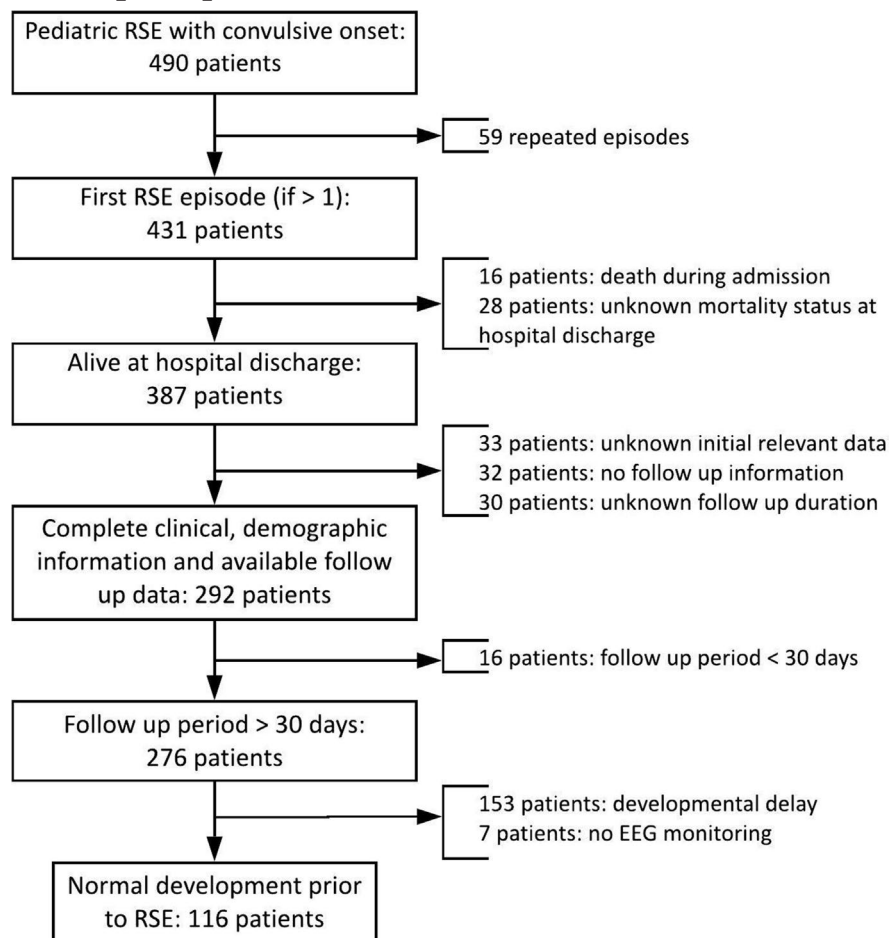


FIGURE 1 Population selection diagram. EEG, electroencephalogram. RSE, refractory convulsive status epilepticus

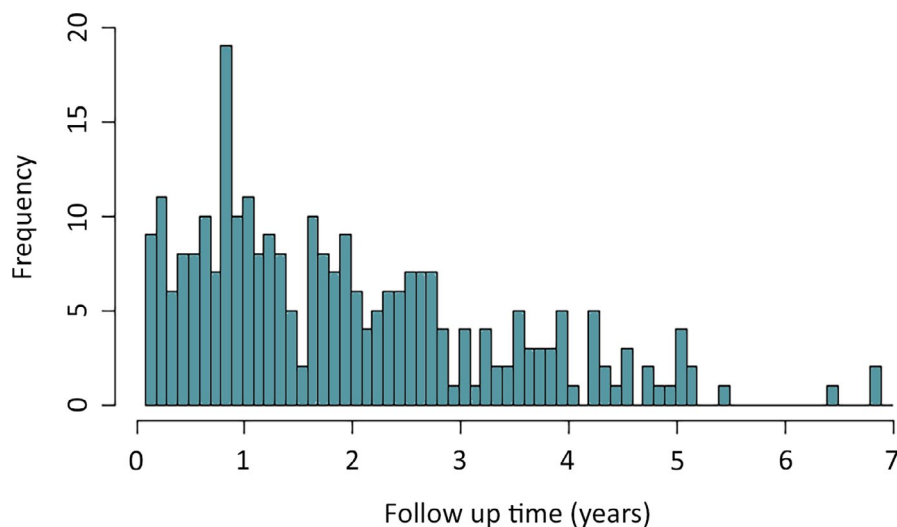


FIGURE 2 Distribution of the follow-up period in the entire cohort (all patients with refractory status epilepticus). The x-axis represents the follow-up period in years, divided over 10% of a year (each bar represents .1 years), and the y-axis represents the frequency as the number of patients per each .1-year range. We followed patients for a median (interquartile range) of 1.6 (.9–2.7) years, ranging from 31 days to 6.9 years

unprovoked seizures. One hundred thirty of the 264 (49.2%) patients had no prior epilepsy at the time of RSE presentation, and 65 (50%) continued to have unprovoked seizures. Patients were more likely to have unprovoked seizures if they had a prior diagnosis of epilepsy compared to those without epilepsy (101/134 [75.4%] vs. 65/130 [50%]; $p < .001$; Figure S2).

3.2.3 | Need for ASMs or rescue medication

At last follow-up, 235 of 265 (88.7%) patients with available information were on ASM. Among 129 patients with no prior epilepsy and available information on ASM use, 102 (79.1%) were on ASM. When compared to patients with no prior epilepsy, patients were more likely to be on

TABLE 1 Demographic and clinical characteristics

Characteristic	Entire RSE population, N = 276	Subgroup with previously normal development, n = 116
Follow-up period, years, median (IQR)	1.6 (.9–2.7)	1.8 (.9–2.7)
Females; males, n (%)	120 (43.5); 156 (56.5)	50 (43.1); 66 (56.9)
Age, years, median (IQR)	4.2 (1.2–8.8)	3 (.8–8.9)
Race, n (%)		
White	180 (65.2)	69 (59.5)
Black or African American	50 (18.1)	29 (25)
Asian	12 (4.3)	6 (5.2)
Arabic	8 (2.9)	1 (.9)
American Indian	1 (.4)	0 (0)
Native Hawaiian	1 (.4)	0 (0)
Not reported/unknown	24 (8.7)	11 (9.5)
Ethnicity, n (%)		
Not Hispanic or Latino	202 (73.2)	85 (73.3)
Hispanic or Latino	47 (17)	16 (13.8)
Not reported/unknown	27 (9.8)	15 (12.9)
Type of RSE, n (%) ^a		
Intermittent RSE	197 (71.4)	89 (76.7)
Continuous RSE	79 (28.6)	27 (23.3)
SE etiology, n (%)		
Unknown	94 (34.1)	40 (34.5)
Structural	76 (27.5)	33 (28.4)
Genetic	58 (21)	8 (6.9)
Other	38 (13.8)	29 (25)
Metabolic	10 (3.6)	6 (5.2)
Past medical conditions, n (%) ^b		
Epilepsy	139 (50.4)	21 (18.1)
Developmental delay	153 (55.4)	0 (0)
Status epilepticus	51 (18.5)	4 (3.4)
Febrile seizures	33 (12)	13 (11.2)
Cerebral palsy	29 (10.5)	0 (0)
None	91 (33)	87 (75)
RSE onset location, n (%)		
Prehospital RSE onset	179 (64.9)	62 (53.4)
In-hospital RSE onset	97 (35.1)	54 (46.6)

Abbreviations: IQR, interquartile range; RSE: refractory convulsive SE; SE, status epilepticus.

^aIntermittent RSE: patient presents with multiple seizures and does not return to baseline. Continuous RSE: ongoing seizure.

^bThese conditions are not mutually exclusive and, therefore, the percentages can add up to more than 100%.

ASM if they had a prior diagnosis of epilepsy (133/136 [97.8%] vs. 102/129 [79.1%]; $p < .001$). Patients were on a median (IQR) number of 2 (1–3.5) ASMs, and this number was higher if patients had a history of epilepsy (3 [2–4] vs. 1 [1–3]; $p < .001$; Figure S2). One hundred thirteen (48.9%) patients had required a rescue medication on at least one occasion.

3.2.4 | Recurrent RSE and prior SE

Fifty-one of 261 (19.5%) patients with complete information about recurrent RSE had a prior SE event before being included in this study. At follow-up, 44 of 261 (16.9%) patients presented with additional RSE episodes. Patients were more likely to have repeated RSE episodes after the sentinel RSE

TABLE 2 RSE etiology and neurological history at the time of RSE, and cause of death of deceased patients during follow-up (>30 days from SE onset and after hospital discharge)

Patient	Underlying RSE etiology	Prior neurological history	New unprovoked seizures/recurrent RSE	Cause of death
1	Acute structural	None	Unknown/yes	Sudden unexpected death in epilepsy
2	Genetic	Developmental delay	Yes/no	GSD Type 1 exacerbation in the setting of acute illness and hypoglycemia
3	Acute structural	None	Yes/yes	Brain tumor (malignant pinealoma)
4	Acute structural	None	No/no	Complications in the context of DiGeorge syndrome
5	Remote structural	None	No/no	Sepsis
6	Unknown	None	Yes/no	Complications in the context of end-stage renal disease and cardiac arrest
7	Genetic	Epilepsy, developmental delay	Yes/no	Sudden unexpected death in epilepsy
8	Remote structural	Epilepsy, developmental delay	Yes/no	Complications in the context of mitochondrial disorder (acute liver failure, progressive anasarca)
9	Genetic	Epilepsy, developmental delay	No/yes	Complications in the context of MERRF and refractory epilepsy (aspiration pneumonia)
10	Other	None	No/no	Respiratory failure in the context of Wiskott–Aldrich syndrome
11	Genetic	Epilepsy, developmental delay	Yes/no	Respiratory failure in the context of <i>POLG</i> mutation
12	Genetic	None	Unknown/unknown	Unknown
13	Genetic	Epilepsy, developmental delay	Unknown/unknown	Unknown
14	Genetic	None	Yes/no	Accidental (drowning)
15	Genetic	Developmental delay	Unknown/unknown	Complications in the context of mitochondrial disorder

Abbreviations: GSD, glycogen storage disease; MERRF, myoclonic epilepsy with ragged-red fibers; *POLG*, DNA polymerase gamma; RSE, refractory convulsive SE; SE, status epilepticus.

event if they had a history of SE; 14 of 49 (28.6%) patients with prior SE presented with repeated RSE episodes during follow-up as compared to 30 of 212 (14.2%) who had no history of SE ($p = .020$).

3.2.5 | Newly discovered etiologies

Information about etiology was not available at follow-up in 20 of 276 (7.2%) patients. Of the patients who had unknown etiology at the time of the event ($n = 86$, 33.2%), at follow-up, 46 (53.4%) remained unknown. Patients who had a newly identified etiology at follow-up included genetic ($n = 17$, 42.5%), structural ($n = 9$, 22.5%), immune ($n = 8$, 20%), infectious ($n = 5$, 12.5%), and metabolic ($n = 1$, 2.5%).

3.3 | Aim 2: Subgroup analysis in patients with normal developmental baseline.

3.3.1 | New neurological deficits

One hundred seven of 116 (92.2%) patients with prior normal development had available information regarding new neurological deficits, and 42 of 107 (39.3%) patients developed new deficits during follow-up. New deficits consisted of cognitive (35, 83.3%), motor (24, 57.1%), and behavioral (26, 61.9%) findings. Thirty-one of 42 (73.8%) patients developed at least two different types of deficits. Underlying RSE etiologies in these 42 patients included structural in 15 (35.7%; acute, $n = 12$; remote, $n = 3$), unknown in 13 (31%), other—that is, febrile SE, central nervous system infection, toxic, autoimmune—in 13 (31%), and genetic in one (2.4%).

Patients with new deficits had a median (IQR) electroclinical RSE duration of 10.3 (2.1–134.5) h versus 4 (1.6–16) h in patients without new deficits ($p = .011$). RSE duration was not normally distributed. Additionally, the proportion of patients receiving a continuous infusion was higher in patients with new deficits (31, 73.8%), as compared to patients without new deficits (35, 53.8%; $p = .043$). The proportion of patients with prior epilepsy was lower in patients with new deficits (3, 7.1%) than in those without new deficits (16, 24.6%; $p = .021$). In multivariate analysis, the only predictor for presenting a new deficit was the electroclinical RSE duration (odds ratio [OR] = 1.003, 95% confidence interval = 1.0008–1.0069, $p = .027$; Table 3). The median (IQR) convulsive RSE duration was 2.3 (.9–18.1) h in patients with new deficits versus 2 (.9–4.5) h in patients without new deficits ($p = .266$). A mediation analysis showed that the time to first BZD was neither a predictor of new deficits ($p = .887$) nor a predictor of electroclinical RSE duration ($p = .466$). Therefore, the RSE duration is not a mediator between time to first BZD and new deficits (Appendix S1).

3.3.2 | Functional outcome by GOS-E score

Ninety of 116 (77.5%) patients had a GOS-E score during the follow-up period. Twenty-two (24.4%) of these had an unfavorable GOS-E score, and 68 (75.6%) had a favorable GOS-E score. The electroclinical RSE duration was not different between the two outcome groups (Table 4). Receiving a continuous infusion was more frequent in patients with unfavorable GOS-E scores when comparing the two groups in univariate analysis (19/22 [86.4%] vs. 37/68 [54.4%],

$p = .010$). This association remained significant after adjusting for potential confounders (Table 4).

4 | DISCUSSION

We followed 276 patients for a median duration of 1.6 years after RSE. Four percent of patients died during the sentinel event hospital admission, and an additional 5.4% of patients died after hospital discharge, mostly in the setting of an underlying medical condition. Fifty percent of patients with no history of epilepsy developed subsequent unprovoked seizures, 89% were on ASM, and almost 50% required rescue medication during the follow-up period. We identified a 16.9% RSE recurrence rate, more frequent in patients with prior SE events. At follow-up, the etiology was newly identified in about half of the patients with an initially unknown etiology. In a subpopulation of patients with previously normal development, 39.3% presented with new neurological deficits and had a median 2.5-fold longer electroclinical RSE duration than patients without new deficits. An unfavorable GOS-E score was independently associated with continuous infusion treatment.

We found a 5.4% mortality rate at long-term follow-up, including two patients with sudden death in epilepsy. This compares to the 7.8% long-term case fatality from the North London cohort including 206 children, which identified an underlying neurological disorder as the major predictor for mortality.¹³ The difference in the mortality rate may be explained by a longer follow-up duration in the cited study (median = 7.8 years) and, potentially, by differences in the severity of underlying etiologies. Convulsive SE duration

TABLE 3 Predictors of new neurological deficits at long-term follow-up in the subpopulation of normally developed patients

Characteristics, $n = 107$	Univariate analysis			Multivariate analysis		
	New deficit, $n = 42$	No new deficit, $n = 65$	p	OR	95% CI	p
Electroclinical RSE duration, h, median (IQR)	10.3 (2.1–134.5)	4 (1.6–16)	.011	1.003	1.0008–1.0069	.027
Continuous infusion, n (%)	31 (73.8)	35 (53.8)	.043	1.74	.68–4.54	.246
Etiology, n (%) ^{a,b}						
Structural	15 (35.7)	16 (24.6)	.276			
Unknown	13 (31)	25 (38.5)	.535	.42	.14–1.25	.128
Others	14 (33.3)	24 (36.9)	.836	.60	.20–1.64	.354
Prior epilepsy, n (%)	3 (7.1)	16 (24.6)	.021	.29	.06–1.06	.085
Age, years, median (IQR)	5.2 (1–9.3)	1.9 (.9–8.3)	.163	1.05	.96–1.14	.256
Sex, male, n (%)	27 (64.3)	34 (52.3)	.237	2.17	.87–5.72	.102

Note: Forty-two (39.3%) patients developed new neurological deficits during the follow-up period. In multivariate analysis, the electroclinical RSE duration was predictive of a new neurological deficit ($p = .027$).

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; RSE, refractory convulsive status epilepticus.

^aIn multivariate analysis, structural was the reference category for the categorical variable etiology.

TABLE 4 Predictors of unfavorable functional outcome (GOS-E score ≥ 4) at long-term follow-up in the subpopulation of normally developed patients

Characteristics, <i>n</i> = 90	Univariate analysis			Multivariate analysis		
	Unfavorable GOS-E score ≥ 4 , <i>n</i> = 22	Favorable GOS-E score < 4 , <i>n</i> = 68	<i>p</i>	OR	95% CI	<i>p</i>
Electroclinical RSE duration, h, median (IQR)	9.3 (1.7–94.5)	3 (1.9–21.9)	.252	1.0004	.997–1.002	.672
Continuous infusion, <i>n</i> (%)	19 (86.4)	37 (54.4)	.010	8.02	2.17–40.4	.004
Etiology, <i>n</i> (%) ^a						
Structural	10 (45.5)	19 (27.9)	.188			
Unknown	5 (22.7)	24 (35.3)	.308	.35	.08–1.35	.140
Others	7 (31.8)	25 (36.8)	.799	.82	.21–3.05	.765
Prior epilepsy, <i>n</i> (%)	1 (4.5)	10 (14.7)	.282	.22	.01–1.65	.209
Age, years, median (IQR)	1.3 (.3–7.8)	4 (1.2–9.3)	.053	.88	.77–.99	.058
Sex, male, <i>n</i> (%)	13 (59.1)	37 (54.4)	.806	1.28	.40–4.28	.678

Note: Twenty-two (24.4%) patients presented with unfavorable functional outcomes during the follow-up period. In multivariate analysis, the use of a continuous infusion ($p = .004$) was a predictor of a GOS-E score ≥ 4 .

Abbreviations: CI, confidence interval; GOS-E, Glasgow Outcome Scale-Extended; IQR, interquartile range; OR, odds ratio; RSE: refractory convulsive status epilepticus.

^aIn multivariate analysis, structural was the reference category for the categorical variable etiology.

was not associated with overall mortality in univariate analysis.¹³ The number of patients who died in our cohort was too small to perform similar analyses and, therefore, we primarily aimed to describe the long-term mortality. A population-based study followed 150 children with childhood onset epilepsy with and without SE over 30 years and found a 16% mortality rate, related to a remote symptomatic etiology in 83%, showing no clear effect of SE on death.³¹ Adult studies also suggested that symptomatic etiologies are a major predictor of long-term mortality.^{7,32} Our results described complications of the underlying medical condition as the most frequent cause of death after discharge, more common in the setting of metabolic disorders. Therefore, consistent with prior studies, the impact of SE on mortality as an independent risk factor remains unclear.

Upon RSE presentation, the etiology was often unknown in our sample (34.1%). Previous studies reported a lower rate of unclassified or cryptogenic causes.^{6,17} However, we used the most recently updated International League Against Epilepsy classification including the category “unknown,” which may partly account for this difference.³³ Our study compiled the testing results regarding the ultimate cause of SE before and during the initial RSE admission, as well as during the follow-up period. Interestingly, of the 86 patients in our cohort who had an unknown etiology during the RSE hospitalization, 46.5% had an underlying etiology identified at follow-up, and genetic causes were most frequently identified (42.5%). The initial diagnostic workup may therefore need to be extended to consider uncommon causes when the etiology is not readily identified. This further evaluation may

include genetic, autoimmune, or metabolic testing, which could delay the diagnosis due to long turnaround times. The ability to identify an etiology with additional testing highlights the importance of extensive etiological evaluation, particularly highlighting advances in genetic testing.

Of the 130 patients with no prior diagnosis of epilepsy, 49.2% had unprovoked seizures during follow-up, and 79.1% were treated with ASM. The risk of developing subsequent epilepsy after SE varies from 5% to 36% in children,⁷ and 87.5% to 100% after RSE in small pediatric and adult series.^{4,34} One prospective study evaluated 134 children with convulsive SE at a median follow-up of 8.9 years and reported a cumulative incidence of subsequent epilepsy of 24.7%.¹¹ This incidence represents half of that reported in our cohort, which may be explained by greater disease severity, as our study included RSE only. In our study, 16.9% of patients presented with repeated RSE episodes, which falls within the range of reported SE recurrence in children in the literature (10%–56%).⁷

A recent review analyzed 37 studies on long-term neurological deficits after SE.⁷ They found that the long-term cognitive sequelae in children vary from 28% to 34%,⁷ in concordance with our 32.7% (35/107) rate. There are very few prospective, long-term outcomes studies in SE patients, including refractory cases. The cited North London study on 134 children found a cumulative incidence of 2.1% for motor disability and 8.8% for intellectual disability.¹¹ A retrospective study of 65 children with SE found that 15% developed neurological sequelae after a mean follow-up of 3.6 years.¹⁹ Another prospective study in 59 adults (15 with RSE), concluded that 46% developed neurological sequelae or died

after 13 months of follow-up.³⁵ A retrospective study analyzed 75 adults with RSE and showed that 29% had neurological deficits at 1-year follow-up.³⁶ Although the populations and methodologies largely differ, our data are in agreement with prior findings.

Several studies aimed to determine predictors for unfavorable outcomes after SE. The population-based North London study evaluating long-term morbidities concluded that a prior diagnosis of epilepsy was the only predictor of intellectual disability.¹¹ Convulsive SE duration analyzed as a continuous and dichotomous variable was not an independent predictor.¹¹ In our study, the only significant predictor for new deficits including cognitive deficits (adjusted for potential confounders) was the electroclinical RSE duration. This factor was not significant when an unfavorable GOS-E score was the outcome measure, which may be related to the difference as an outcome and a smaller sample size for this secondary outcome. One potential explanation for differences between our results and the North London study may relate to our focus on a subgroup of developmentally normal patients at baseline. We also analyzed the duration as a continuous variable and included the electrographic duration of the RSE. Conversely, the North London study analyzed the convulsive SE duration as a dichotomous variable (30–60 min or >60 min). Remarkably, differences in SE duration from 40 to 60 min may not be as relevant for the outcome as differences from 60 to 120 min or longer, which may contribute to worse outcomes, including brain damage.³⁷

A few other studies have also found an association between SE duration and long-term outcomes. A retrospective study in 65 children found that patients with SE lasting longer than 2 h, evaluated both clinically and by EEG, had 68.8% of neurological sequelae as compared to 32.7% ($p < .025$) in patients with SE lasting less than 2 h.¹⁹ Another retrospective study followed 225 children with SE for a mean of 64 months.²³ The main predictor for poor outcome was an acute symptomatic and progressive etiology; however, after excluding those cases, the main predictor was SE duration longer than 2 h.²³ Longer convulsive SE duration was related to delayed first-line treatment in pediatric RSE.^{27,38} However, in our data, the mediation analysis did not show a correlation of the time to first BZD and the electroclinical RSE duration. Moreover, the time to first BZD did not predict the development of new deficits, neither directly nor indirectly when considering a longer RSE duration. Other modifiable factors potentially affecting RSE duration, such as type of treatments or time to second- or third-line treatments, could ultimately be impacting long-term outcomes in more refractory cases. In a retrospective study in 75 adult patients, the main predictors for developing a neurological deficit at follow-up were older age and progressive or fatal etiologies.³⁶ Another prospective study followed for 2.7 years a group of 60 previously developmentally normal children with

electrographic seizures or SE.²⁰ Patients with electrographic SE were more likely to develop subsequent epilepsy and had worse GOS-E score, after controlling for pediatric intensive care unit (ICU) duration of stay, EEG background, age, and acute neurological disorder.²⁰ In our study, the electroclinical RSE duration was an independent risk factor for worse neurological outcomes, unlike the convulsive duration alone. Thus, the impact of the electrographic component on neurological deficits may potentially highlight the importance of timely EEG monitoring in patients with RSE. Finally, another way of analyzing SE duration, when they are intermittent or non-convulsive, is seizure burden. This has also been associated with poor short-term outcomes in critically ill children and long-term outcomes in adults who had SE after subarachnoid hemorrhage.^{39,40} The pediatric cohort showed increased odds of developing a disability at 3 months or death for every hour of seizure on the continuous EEG.³⁹ Likewise, our results highlighted the relationship between electrographic SE and poor long-term outcomes.

Prior studies also suggested a correlation between the use of continuous infusion for treating SE and unfavorable outcomes, although the relationship of outcomes with the severity of disease in patients treated with continuous infusions or with the use of continuous infusions independently is unclear.⁴¹ Recent studies investigated the relationship between mortality and functional outcomes after treating SE with continuous infusions. A study including 406 adults concluded that the use of continuous infusion in SE was associated with increased mortality and unfavorable functional outcome (GOS-E = 1–3) after adjusting for confounders through propensity score matching.⁴² A retrospective pediatric study showed an association between pentobarbital infusion duration and functional decline at discharge, which did not hold after adjusting for the baseline neurologic function.⁴³ Prior pSERG analyses identified that patients receiving continuous infusions had longer ICU length of stay, failure to return to baseline, and higher mortality after adjusting for potential confounders.⁴⁴ In our study, receiving at least one continuous infusion showed an independent association with an unfavorable GOS-E. However, we could not control for the duration and cumulative dose of continuous infusions or patient severity of disease; therefore, these results need to be interpreted cautiously, given the potential for confounding by indication.

Results need to be interpreted in the setting of data acquisition, including selection and information bias, more severely affected patients being admitted to tertiary or quaternary hospitals. The population size and a large number of sites prevented us from accounting for different hospital treatment variability. We did not prospectively capture patient severity scores (e.g., Pediatric Risk of Mortality score) or seizure severity scores at RSE onset, but we were able to include SE duration as a marker for severity. The electroclinical RSE duration was based on EEG monitoring in all

patients, although the exact time of placement or the duration of EEG monitoring was not available and may not be uniform between patients. Moreover, we lack a central interpretation of EEG monitoring, which may lead to subjective interpretations of findings. Variability in the follow-up duration does not provide further details regarding the timing and appearance of long-term outcomes. We observed patients at one specific time point and were unable to follow neurological outcomes over time. Also, other than neurological history and examination, no detailed testing was deployed to determine the development or the presence of new deficits at follow-up. However, the focus on patients with no clear deficits at baseline and the variability of care through diverse management protocols among sites strengthen our results. To note, certain disabilities may appear later during neurodevelopment and may develop during follow-up as patients age, independently from RSE.

Furthermore, we described several long-term outcomes in a larger sample as compared to similar studies, such as mortality after discharge. In some cases (such as genetic diseases, tumors, etc.), mortality was difficult to attribute to RSE itself and often related to an underlying condition. Despite overall large numbers, analyses with more granular categories on RSE etiologies were not possible, as subgroups become too small. Furthermore, although we identified an association with electroclinical RSE duration and poor long-term outcomes, our data abstraction may have excluded relevant clinical confounders, and the small size of the adjusted OR (1.003) may be interpreted in the context of the RSE duration unit (hours) and its clinical significance. We followed the patients based on their medical records, as we did not have the resources to interview the patients to obtain complete follow-up information or to apply standardized neuropsychological analyses. Thus, we lack more detailed information about the type and severity of the new deficits.

5 | CONCLUSIONS

After an RSE episode and a median follow-up of 1.6 years, the postdischarge mortality rate was 5.4%. Half of the patients with no prior epilepsy developed recurrent unprovoked seizures. Among patients with no prior epilepsy, 80% were on ASM during follow-up. Nearly 17% of patients presented with repeated RSE, and half of the patients required at least one rescue medication during follow-up. Among the subgroup of previously normally developed patients, close to 40% of patients had new neurological deficits. The development of new neurological deficits at follow-up was correlated with the electroclinical RSE duration, and an unfavorable GOS-E score was associated with the use of continuous infusions. These factors may inform future preventative and interventional strategies.

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CONFLICT OF INTEREST

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financial benefits from this technology in the form of compensation in the future. He has received research support from the Epilepsy Research Fund, the NIH, the Epilepsy Foundation of America, the Epilepsy Therapy Project, and the Pediatric Epilepsy Research Foundation, research grants from Lundbeck, Eisai, Upsher-Smith, Mallinckrodt, Sunovion, Sage, Empatica, and Pfizer, and past device donations from various companies, including Empatica, SmartWatch, and Neuro-electrics. He served as a consultant for Zogenix, Upsher-Smith, Amzell, Engage, Elsevier, UCB, Grand Rounds, Advance Medical, and Sunovion. He performs video-electroencephalographic long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies at Boston Children's Hospital and affiliated hospitals and bills for these procedures, and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums/travel support from national societies including the American Academy of Neurology, American Epilepsy Society, and American Clinical Neurophysiology Society, and for grand rounds at various academic centers. His wife, Dr. Karen Stannard, is a pediatric neurologist, and she performs video-electroencephalographic long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies and bills for these procedures, and she evaluates pediatric neurology patients and bills for clinical care. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

Marina Gaínza-Lein participated in drafting and revising the manuscript for content, including medical writing, study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, and study supervision or coordination. Cristina Barcia Aguilar participated in drafting and revising the manuscript for content, including medical writing, study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, and study supervision or coordination. Juan Piantino participated in revising the manuscript for content, including medical writing, study concept and design, data acquisition, and study supervision or coordination. Kevin E. Chapman participated in revising the manuscript for content, including medical writing, study concept and design, data acquisition, and study supervision or coordination. Iván Sánchez Fernández participated in revising the manuscript for content, including medical writing, study concept and design, data acquisition, and study supervision or coordination. Marta Amengual-Gual participated in revising the manuscript for content, including medical writing, study concept and design, data acquisition, and study supervision or coordination. Anne Anderson participated in revising the manuscript for content, including

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DATA AVAILABILITY STATEMENT

Supplementary data are available in GitHub at <http://github.com/CristinaBarcia/pSERG-LTO>. All statistical analyses and results are available in GitHub (Appendix S1).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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