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SUPPLEMENT ARTICLE

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Long-term outcomes of status epilepticus: A critical assessment

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Summary

We reviewed 37 studies reporting long-term outcomes after a status epilepticus (SE) episode in pediatric and adult populations. Study design, length of follow-up, outcome measures, domains investigated (mortality, SE recurrence, subsequent epilepsy, cognitive outcome, functional outcome, or quality of life), and predictors of long-term outcomes are summarized. Despite heterogeneity in the design of prior studies, overall risk of poor long-term outcome after SE is high in both children and adults. Etiology is the main determinant of outcome, and the effect of age or SE duration is often difficult to distinguish from the underlying cause. The effect of the treatment on long-term outcome after SE is still unknown.

KEYWORDS
cognitive outcome, epilepsy, functional impairment, mortality, neurological sequelae, quality of life

1 | INTRODUCTION

Status epilepticus (SE), especially refractory SE (RSE), is a life-threatening condition often requiring intensive care.[1-4] Long-term sequelae may include neurological, cognitive, and behavioral impairments and decline in quality of life (QoL),[4,5] and impose heavy burdens on the patient, the caregivers, and the healthcare system. Outcomes are influenced by type of epilepsy, type of SE, etiology, SE duration, and patient's age.[4] This review aims to provide an overview of long-term outcomes in patients with SE.

2 | LITERATURE SEARCH

We performed a search of the medical literature using the following strategy in PubMed: ("status epilepticus") AND ("long-term outcome" OR "long-term mortality" OR "long-term morbidity" OR "quality of life"), gathering 570 articles. Our search was restricted to full-length clinical studies in humans written in the English language until December 1, 2017. We excluded studies focusing on the neonatal period (1-28 days of postnatal age at the beginning of SE) and studies evaluating solely short-term outcome or very specific subgroups of patients. In addition, we added relevant articles from the reference lists of articles from the primary search. We included the results of 37 relevant studies, 16 on children (Table 1), 14 on adults and seven on a mixed population of adults and children (Table 2), reporting long-term outcomes after SE (ie, after hospital discharge or >1 month from SE onset), and reviewed studies for predictors of outcome (Figure 1).

3 | DEFINITIONS

In 15 pediatric studies, SE was defined as any seizure lasting >30 minutes or recurrent seizures lasting a total of >30 minutes without the subject fully regaining consciousness by most studies, except for one paper that used a 5-minute limit.[6] In 21 studies including adults, definitions were more variable, including 30-minute seizure duration limits,[7-13] and 5-minute clinical seizure duration or more than two seizures without return to baseline between seizures.[14-19] One study also chose a 10-minute clinical seizure duration cutoff limit.[20] Two studies reported patients with prolonged refractory SE, including patients with SE that persists or recurs over a period of ≥7 days after the initiation of continuous general anesthesia.[21,22] Super-refractory SE (SRSE) was defined as SE that continues or recurs ≥24 hours after the onset of anesthesic therapy, including those cases that recur on the reduction or withdrawal of anesthesia.[23] Of note, the definition of RSE was also variable, but usually referred to SE that continues after administration of a benzodiazepine and a second antiseizure medication. One study defined RSE as SE lasting >60 minutes.[24]

4 | APPROACH TO INTENSIVE CARE UNIT TREATMENT OF SE

Treatment of SE mostly follows general treatment guidelines and algorithms.[1,2] The first line usually consists of benzodiazepines, often followed by intravenous nonbenzodiazepine antiseizure medications (ASMs). If SE continues and becomes refractory, guidelines recommend transfer to the intensive care unit and additional anesthetic treatment, ideally within 30 or 40 minutes after SE onset.[1,2,25] The most common drugs at this treatment stage are continuous infusions of midazolam, infusions of pentobarbital/thiopental, or intermittent phenobarbital doses.[1] Main adverse events may include respiratory depression and hypotension, and thus mechanical ventilation and blood pressure management are often needed.[25] Currently, class I evidence supports the use of benzodiazepines as first-line treatments, and a major randomized controlled trial is in progress in an attempt to obtain data supporting choices of second-line treatment (Established Status Epilepticus Treatment Trial). Limited data support third-line treatment choices.[2]

Key Points

- Long-term outcomes in patients with status epilepticus are predicted by underlying etiology
- Long-term mortality after status epilepticus is seen in up to 20% of children and 55% of adults
- Status epilepticus is associated with increased rates of status epilepticus recurrence, subsequent epilepsy, and worsening of previous epilepsy
- Further studies using standardized tools are in progress to assess quality of life and functional and cognitive outcome
- Promising research suggests that functional outcome may improve over time

5 | LONG-TERM OUTCOMES OF SE

5.1 | Subsequent epilepsy

The risk of subsequent epilepsy after SE is high in both children and adults, with highest onset risk during the first year of follow-up.[4] In pediatric patients, this risk ranges from 5% to 36%.[6,26-29] In mixed populations of adults and children, subsequent epilepsy after SE may occur in 22%-41%,[14,30] which is less than in patients with history of RSE, who have a 87.5% risk of subsequent epilepsy.[14] Only one adult study showed that 31% of patients have subsequent epilepsy or worsening of previous epilepsy after SE.[20] The main predictor of subsequent epilepsy is the underlying SE etiology, and nonfebrile-nonidiopathic,[28] remote symptomatic,[29] structural, and acute symptomatic (eg, anoxic brain injury)[30] etiologies are usually associated with higher risk. In comparison, the risk of subsequent epilepsy after a single seizure is 40%-50%.[31,32] In terms of epilepsy severity after SE, epilepsy becomes refractory in 15%-25% of children after SE, which is not markedly different from the proportion of refractory cases in the general

TABLE 1 Pediatric studies on long-term outcome after SE

Authors, study design	Year	Population	Follow-up testing/ scores	Mortality rate	Outcome: epilepsy	Outcome: cognitive abilities	Outcome: QoL	Outcome: functional outcome/other	Predictors
Chevrie & Aicardi,[38] prospective	1978	Children 28 d-1 y, n = 313, SE: n = 40	>1 y, median 3 y, no formal testing	22%, patients with SE	N/A	Severe intellectual disability in SE: 60%	N/A	Neurological sequelae in SE: 43%	Cognitive abilities; poor outcome: symptomatic cases, age < 6 mo; good outcome: positive family history; functional outcome: pre- or perinatal abnormality
Maytal et al,[26] retrospective and prospective	1989	Children in SE, n = 193	13.2 mo, no formal testing	3.6%, at 3 mo	New epilepsy: 30%	N/A	N/A	Neurologic deficits, motor or cognitive: 9.1%	Functional outcome: duration of SE (in the acute symptomatic group), etiology (acute or progressive insults)
Shinnar et al,[35] prospective	1992	Children with first SE, n = 95	29 mo, no formal testing	3 died within 10 d	Recurrence: 17%	N/A	N/A	No deterioration in neurological function	Recurrence: underlying neurological abnormality, etiology (remote symptomatic and progressive causes)
Eriksson & Koivikko,[27] retrospective	1997	Children in SE, n = 65	3.6 y	0%	New epilepsy: 23%	N/A	N/A	Neurological sequelae: 15%	Functional outcome: SE duration > 2 h
Barnard & Wirrell,[28] retrospective	1999	Children in SE, n = 47	53 mo, developmental quotient	15.4%	New epilepsy: 36%; recurrent seizures: 85%; refractory epilepsy: 25%; recurrent SE: 50%	Neurodevelopmental deterioration: 34% (26%: severe)	School: normal (6%), resource assistance (14%), teaching aides (37%), special class (43%); behavior problems: 41%	Neurological sequelae: 79% (mild: 21%, moderate: 28%, severe: 34%)	Functional outcome: etiology (nonfebrile-nonidiopathic), perinatal difficulties, developmental delay, abnormal neurologic examination; abnormal neuroimaging; developmental deterioration: etiology, neuroimaging, young age; epilepsy: etiology

(Continues)

TABLE 1 (Continued)

Authors, study design	Year	Population	Follow-up testing/ scores	Mortality rate	Outcome: epilepsy	Outcome: cognitive abilities	Outcome: QoL	Outcome: functional outcome/other	Predictors
Kim et al,[24] case series	2001	Children in RSE treated with pentobarbital, n = 23	4 y	43.5%, in hospital	N/A	N/A	N/A	Neurological sequelae: 61.5%	Mortality: failure of seizure control after PB coma, acute symptomatic etiology; functional outcome: treatment delayed
Tabarki et al,[36] retrospective	2001	Children in SE, n = 139	3.5 y, no formal testing	15.8%, within 2 mo	Epilepsy without cognitive deterioration: 5%	Moderate intellectual disability: 11.5%; severe: 19.5%; remission: 48%	N/A	N/A	Functional and cognitive outcome: etiology (remote symptomatic and progressive encephalopathy > acute symptomatic > febrile and idiopathic); age < 1 y
Sillanpää & Shinnar,[34] prospective	2002	Children with childhood onset epilepsy, n = 150, 27% with SE, n = 41	30 y	16%	Recurrence of SE: 56%; remission: 55% (compared to 80% in children without SE)	N/A	Comparing SE or not: similar social and educational outcome	N/A	Mortality and social outcome: occurrence of SE did not alter mortality rate and social and educational outcome; remission rates: slightly affected by SE
Metsäranta et al,[6] retrospective	2004	Children in SE, n = 186	2 y and 1 mo, no formal testing	0%	New onset epilepsy: 22%	N/A	N/A	Permanent neurological sequelae: 2.2%, temporary sequelae: 3.2%	Minor neurological sequelae: duration of seizure; major neurological sequelae: acute symptomatic cause; temporary sequelae: febrile SE

(Continues)

TABLE 1 (Continued)

Authors, study design	Year	Population	Follow-up testing/ scores	Mortality rate	Outcome: epilepsy	Outcome: cognitive abilities	Outcome: QoL	Outcome: functional outcome/other	Predictors
Maegaki et al,[17] retrospective	2005	Children in SE, n = 234	64 mo, no formal testing	4%	N/A	N/A	N/A	Neurological sequelae: 15%	Mortality/functional outcome: etiology (acute neurological insult and progressive neurological disease), seizure duration (>2 h), asthmatic attack
Hussain et al,[29] retrospective	2007	Children in SE, n = 137	1.5 y, no formal testing	0%	New epilepsy: 5%; recurrence of SE: 10%	N/A	N/A	Neurological sequelae among previously normal children: 1.4%	New epilepsy: remote symptomatic group, no correlation with duration of SE
Wagenman et al,[45] prospective	2014	Children with acute neurologic disorders neurodevelopmentally normal before PICU admission with ES or ESE, n = 137	2.7 y, GOS-E Peds and PedsQoL	0%	Subsequent seizures: 35%	N/A	PedsQoL: median = 94 for SE and 62 for ESE	Unfavorable outcome GOS-E Peds: 35%	Functional impairment: ESE; subsequent seizures: ESE
Pujar et al,[53] prospective	2011	Children with convulsive SE, n = 206	8 y	3% within 1 mo, 11% within 8 y	N/A	N/A	N/A	N/A	Mortality: preexisting clinically significant neurological impairments; better outcome: prolonged febrile convulsions and idiopathic convulsive SE
Camfield & Camfield,[33] retrospective	2012	Children with focal epilepsy and normal intelligence (acute symptomatic causes not included), n = 188 (20% SE)	Mean 27 y, wide variety of testing	0%	Seizure-free: 61.5% with SE vs 66.4% without SE; intractability: 15% vs 11.4%	Learning disorders: 28 with SE vs 33% without SE	N/A	N/A	Cognitive outcome and epilepsy: no difference between the SE and non-SE groups

(Continues)

TABLE 1 (Continued)

Authors, study design	Year	Population	Follow-up testing/ scores	Mortality rate	Outcome: epilepsy	Outcome: cognitive abilities	Outcome: QoL	Outcome: functional outcome/other	Predictors
Martinos et al,[37] prospective	2013	Children from 1 to 42 mo, in SE (febrile or not), n = 54	At 6 wk and 1 y, Bayley Scales of Infant Development III	1 patient died during follow-up	N/A	Cognitive composite: FSE, 93; non-FSE, 74; control, 107; language composite: FSE, 91; non-FSE, 75; control, 114	N/A	Motor composite: FSE, 96; non-FSE, 77; control, 103	Developmental outcome: nonfebrile SE < FSE < controls
Ferro et al,[5] retrospective	2014	Children with newly diagnosed epilepsy, n = 374 (SE: 6.1%)	24 mo, Quality of Life in Childhood Epilepsy Score	0%	N/A	No cognitive deterioration	Poorer QoL in children with SE	N/A	N/A

ES, electrographic seizure; ESE, electrographic SE; FSE, febrile status epilepticus; GOS-E, Glasgow Outcome Scale–extended; GOS-E Peds, pediatric Glasgow Outcome Scale–extended; N/A, nonapplicable; PB, pentobarbital; PedsQoL, Pediatric Quality of Life Inventory; PICU, pediatric intensive care unit; QoL, quality of life; RSE, refractory SE; SE, status epilepticus.

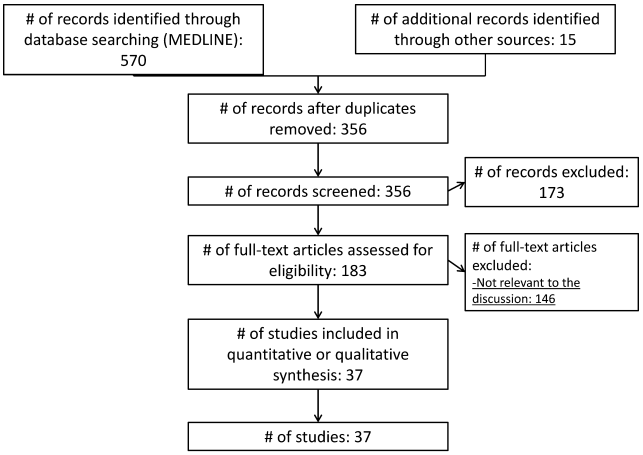

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram of the literature search

epileptic population.[6,33] In a population-based series of 115 children with epilepsy, those who had SE, when compared with those who did not have an SE event, had a lower probability of epilepsy remission (55% vs 80%; risk ratio = 0.58, 95% confidence interval = 0.34-0.99, $P = 0.044$). The patient who had SE also had a lower probability of epilepsy remission off ASMs (39% vs 65%; risk ratio = 0.50, 95% confidence interval = 0.27-0.95, $P = 0.029$),[34] suggesting a more refractory epilepsy in these patients.[33,34] In contrast, a study of 188 children with focal epilepsy found no statistically significant difference in the probability of epilepsy remission off ASM in patients who have SE events (61% in patients with SE vs 66% in patients without SE, $P = 0.5$).[5]

5.2 | Recurrence of SE

In patients with SE, the occurrence of recurrent SE ranges from 10% to 56% in children[28,29,34,35] and from 13% to 37% in mixed population of adults and children.[8,9] Predictors of recurrent SE include age < 4 years,[8] female gender, nonresponse to first ASM for SE,[9] and remote symptomatic and progressive etiologies.[9,35]

5.3 | Cognitive outcome and functional outcome

Cognitive, functional, and QoL sequelae are frequent, especially in RSE and SRSE.[16,20] Long-term cognitive sequelae occur in 28%-34% of children.[28,33,36,37] In one adult study on long-term cognitive sequelae after SE, no cognitive decline was found after 3 years of follow-up, but this series included only 15 patients.[10] Cognitive outcomes are usually evaluated based on clinical judgment or measured using a wide variety of neuropsychological tests. The underlying etiology is the main factor associated with long-term

TABLE 2 Adult or adult and pediatric studies on long-term outcome after SE

Authors, study design	Year	Population	Follow-up testing/scores	Mortality rate	Outcome: epilepsy	Outcome: functional outcome/other	Predictors
DeLorenzo et al,[13] retrospective and prospective	1992	Adults and children in SE, n = 546	7 y	Children: 2.3%, adults: 25%	N/A	N/A	Mortality: etiology (tumor, hematological disease, anoxia, metabolic and congenital malformation), age, SE duration (for short-term mortality)
DeLorenzo et al,[8] prospective	1996	Adults and children with a first SE, n = 166	2 y	Children: 3%, adults: 26% (at 30 d)	Recurrence of SE at 2 y: 13.3%	N/A	Mortality: SE duration, etiology (hypoxia); recurrence: age
Hesdorffer et al,[30] retrospective	1998	Adults and children; acute symptomatic SE vs seizures, n = 416	10 y	N/A	New unprovoked epilepsy: 41% in the SE group vs 13% in non-SE group	N/A	Epilepsy: SE, etiology (anoxia, structural or metabolic cause)
Logroscino et al,[55] retrospective	2002	Adults and children, n = 145	30 d to 12 y	43% (at 10 y)	N/A	N/A	Mortality: SE duration, etiology (acute symptomatic cause), myoclonic SE
Holtkamp et al,[14] retrospective	2005	Adults and children (11-94 y) in SE, n = 79	Unclear, telephone calls (only for "de novo" SE)	RSE: 16.7%; SE, 8.6% (in hospital)	New symptomatic epilepsy: 22% in SE and 87.5% in RSE	N/A	Epilepsy: RSE predicted by encephalitis
Adachi et al,[10] prospective	2005	Adults in SE (n = 15) or with epilepsy (n = 40)	3.2 y, IQ and Weschler Adult Intelligence Scale	0%	N/A	No cognitive decline	Cognitive abilities: no influence of age, CPSE, GCSE, SE duration, etiology (AED withdrawal or unknown)
Hesdorffer et al,[9] retrospective	2007	Adults and children with a first afebrile SE, n = 183	10 y	Unclear	Recurrence: 37% (30% among 30-d survivors)	N/A	Recurrence: female gender, failure to respond the first drug administrated, progressive symptomatic cause
Logroscino et al,[11] retrospective	2008	Adults, unprovoked epilepsy (n = 291) or SE (n = 16)	10 y	9% without SE vs 31% with SE	N/A	N/A	Mortality: age, development of subsequent epilepsy

(Continues)

TABLE 2 (Continued)

Authors, study design	Year	Population	Follow-up testing/scores	Mortality rate	Outcome: epilepsy	Outcome: functional outcome/other	Predictors
Cooper et al,[15] retrospective	2009	Adults with PRSE, n = 14	Median of 313 d, mRS	43% (in hospital), 57% (last follow-up)	N/A	No change for 2 patients and improvement for 4 patients (mRS change: −1)	None
Legriel et al,[20] prospective	2010	Adults in SE, n = 248	90 d, GOS	18.8% (4 patients died during the follow-up)	New epilepsy or worsening of previous epilepsy: 33.5%	Neurological sequelae (GOS = 2-4): 38.8%	Functional impairment (GOS < 5): older age, focal neurological signs, RSE, cerebral insults, SE duration
Ristić et al,[12] prospective	2010	Adults in SE, n = 750	12 y	16% (short term), 22% (long term)	N/A	N/A	Mortality: etiology (progressive and acute symptomatic), age, epilepsy, initial SE
Kilbride et al,[21] retrospective	2013	Adults in PRSE, n = 63	At least 6 mo, mRS	34% (in hospital) and 5 died during follow-up	Seizure-free: 20%; no recurrence	Good outcome: mRS ≤ 3: 22%; mRS = 1: 10%	Functional outcome: normal neuroimaging and a reactive EEG at SE onset
Li et al,[23] case series	2014	Adults in SRSE, n = 13	Median 17 mo, GOS	36.3% (at 3 mo); 15.4% (in hospital)	50%	At 3 mo: mean GOS = 4.1; at 17 mo: mean GOS = 4.6	Functional outcome at 3 mo: etiology (encephalitis), longer period of anesthesia
Jayalakshmi et al,[16] retrospective	2014	Adults and children, n = 177	6 mo, GOS	19%	N/A	Good outcome (GOS = 4-5): SRSE, 33%; non-RSE, 79%; RSE, 57%	Functional outcome: SRSE predicted by presumed encephalitis
Lai et al,[54] retrospective	2015	Adults in PRSE, n = 78	1 y, telephone calls (mRS)	52%	N/A	Poor outcome (mRS = 4-6): 67%	Functional outcome (mRS = 4-6): vasopressor use
Madzar et al,[44] retrospective	2016	Adults in RSE, n = 65	12 wk, mRS	18% (in hospital)	N/A	mRS > 2: 61%	Poor functional outcome: STESS ≥ 3, longer RSE duration (10 d), sepsis
Legriel et al,[43] retrospective	2016	Adults in SE, n = 268	90 d, GOS	13.8% (in hospital); 14.1% (at 90 d)	N/A	Good outcome (GOS = 5): 46%	No association with hypothermia

(Continues)

TABLE 2 (Continued)

Authors, study design	Year	Population	Follow-up testing/scores	Mortality rate	Outcome: epilepsy	Outcome: functional outcome/other	Predictors
Kortland et al,[18] retrospective	2017	Adults in SE, n = 81 (RSE: n = 33)	3 mo, mRS, QOLIE-31, NDDI-E	0%	Hospitalization due to epilepsy: 22.2%	mRS = 0-3: 60.8% (RSE: 70%); major depression: 32.8% (QOLIE-31: SE: 43.5%, RSE: 42.5%)	N/A
Atmaca et al,[19] prospective	2017	Adults in SE, n = 59 (RSE: n = 15)	13.6 ± 4.6 mo	31%	N/A	Poor outcome (death or neurological sequelae): 46%	Mortality and functional outcome: potentially fatal etiology, EMSE score > STESS, mSTESS
Kantanen et al,[58] retrospective	2017	Adults in RSE, n = 395	1 y	25%	N/A	N/A	Mortality: older age, SOFA score, dependence of activities in daily living, SRSE
Kantanen et al,[59] retrospective	2017	Adults in RSE, n = 75 (SRSE: 21%)	1 y, mRS	23 (at 1 y); 7% (in hospital)	N/A	Neurological deficits: 29%; mRS = 4-6: 52%	Mortality: older age

AED, antiepileptic drug; CPSE, complex partial SE; EEG, electroencephalogram; EMSE, epidemiology-based mortality in SE; GCSE, generalized convulsive SE; GOS, Glasgow Outcome Scale; IQ, intelligence quotient; mRS, modified Rankin Score; mSTESS, modified STESS; N/A, nonapplicable; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; PRSE, prolonged refractory SE; QOLIE, Quality of Life in Epilepsy; RSE, refractory SE; SE, status epilepticus; SOFA, Sequential Organ Failure Assessment; SRSE, super-refractory SE; STESS, Status Epilepticus Severity Score.

cognitive outcome in children,[6,28,33,36,38] with symptomatic SE[28,36,38] or progressive encephalopathy[36] contributing to increased risk. Other factors are young age at the time of SE[28,36,38] and neuroimaging abnormalities[28] (Table 1). Also, seizure burden in uncontrolled epilepsy, rather than SE, is more frequently associated with poor cognitive outcome.[39,40]

The impact of SE on cognitive outcome is debatable. Animal models show that prolonged seizures result in neuronal loss and brain connectivity changes.[41,42] A clinical study showed that children with SE had worse long-term cognitive outcome than healthy controls, with nonfebrile SE associated with worse cognitive impairments than febrile SE.[37] In contrast, large studies showed no difference in cognitive outcome when comparing children with and without SE, although controls in this study were children with epilepsy.[33,34] Most adult studies focus on functional rather than cognitive outcomes using standardized scales like the modified Rankin Score and the Glasgow Outcome Scale, with functional deficits seen in 21-61%,[16,20,21,43,44] and these could be more severe in RSE[20] or SRSE (67%).[16] Functional outcomes in children are mostly based on clinical impression, yielding a wide spectrum of functional impairment after SE from 0% to 79%,[6,17,24,26–29,35,36,38,45] and this range may also be related to different definitions and assessment of impairment, and often lack of good baseline information. The evaluation of long-term cognitive outcomes is further complicated by evolution over time in some cases, and in particular outcomes in children are often not static as development progresses. In a pediatric study, impaired performance at discharge persisted at 1 year,[37] whereas in another series deficits disappeared or improved over time.[15,22,46] Predictors of poor functional outcome include etiology (nonfebrile SE, acute symptomatic SE, progressive encephalopathy)[17,26,28,36,37] and SE duration[17,26,27,45] (Table 1).

5.4 | QoL

There is limited literature on QoL after SE. Compared to short seizures, convulsive or electrographic-only SE[45] has a negative impact on the long-term QoL.[5] However, population-based studies comparing adults with childhood-onset epilepsy with or without SE showed no association with educational attainment, employment status, and income.[33] Patients after RSE may achieve an equivalent QoL as compared to patients after non-RSE.[18] However, patients in seizure remission present better QoL results as compared to patients with SE.[18] Other prospective studies showed only small associations between SE and selected domains of QoL.[34,47]

5.5 | Mortality

Short-term mortality of SE ranges from 0% to 4%[26,48,49] in children and 2%-40% in adults, with higher mortality in RSE.[26,48,50-52] Long-term mortality data after an episode of SE, including in-hospital deaths, is 0%-22% in children[5,6,17,26–29,33–35,37,38,45,53] and 0%-57% in adults.[10-12,17,19,20,43,54] Although long-term mortality rates are high, the underlying etiology and the period of follow-up are major determinants of outcome. A population-based study reported 24 deaths among 150 patients with childhood onset epilepsy, but mortality was similar in those with or without prior SE.[34] A prospective study including 206 children identified preexisting neurological comorbidities as a predictor of mortality.[53] Risk factors for mortality in adults include etiology (progressive, remote, or acute symptomatic causes),[8,12,13,24,55] older age,[11,12] SE duration,[8,13,56] and development of subsequent epilepsy.[11] The Status Epilepticus Severity Score is a valuable tool to assess in-hospital mortality but has not been clearly validated to estimate long-term mortality.[57-59] The Epidemiology-Based Mortality in Status Epilepticus score considers etiology, age, electroencephalogram, and comorbidities and has been associated with poor long-term outcome in one prospective study.[19]

5.6 | Health care utilization and cost

There are limited data on short-term resource utilization in SE. Studies on mean SE cost estimated up to US$18 834 in the USA and up to €14 946 in Germany per admission, significantly higher than those related to admissions of patients with epilepsy (€1998-€3475).[56,60,61] However, these studies reflect the in-hospital treatment, but SE is also associated with indirect costs because of unfavorable outcomes and costs or tentative income loss for those caring for patients with epilepsy.[62] Surprisingly, there is a lack of studies on long-term resource utilization due to SE.

6 | DIFFERENCES BETWEEN ADULT AND PEDIATRIC POPULATION

Age is one of the main outcome predictors after SE,[53] with the youngest (<1 year)[13,28,36,38] and oldest[11,12,20] patients having the poorest long-term outcomes (>65 years[11] or odds/risk ratio = 1.04-1.05/year[12,20]). The higher mortality reported in younger children may also reflect the higher proportion of acute symptomatic cases in this age group.[63-65] Of note, animal models have shown that immature neurons are more resistant to neuronal damage after a prolonged seizure.[66,67] This may be reflected in the finding that children have fewer cognitive sequelae of SE and lower mortality than adults.[13,68] However, sequelae in children usually affect a longer expected lifespan than in adults and the elderly.[69]

7 | FACTORS AFFECTING OUTCOME

7.1 | SE etiology

As in short-term studies, etiology is the main determinant of long-term morbidity and mortality related to SE, probably more than the SE episode itself.[33,34,55] A large majority of studies assigned the etiology of SE into broad categories (acute symptomatic, progressive symptomatic, remote symptomatic, and idiopathic/cryptogenic) based on previous work and International League Against Epilepsy recommendations,[70] but the category assignments may in part contain information bias, and various classifications are used.

In adults, etiologies associated with poor outcome include hypoxia,[7,8,13] acute symptomatic,[12,20,44,45,55] and progressive symptomatic causes.[9,12] In children, many studies have pointed out remote[29,35,36] and acute[6,17,24,26,71] symptomatic causes, progressive encephalopathies,[17,26,35,36] or more extensively "nonfebrile-nonidiopathic SE"[28] as predictors of poor outcome. In contrast, the risks of mortality[53] and neurological deficits are low with febrile SE and cryptogenic/idiopathic SE.[26-28,72] However, the specific subcategory of presumed encephalitis or new onset refractory SE may be associated with worse long-term outcome[16,73,74] and prolonged duration of SE.[21]

7.2 | Treatment

There is not sufficient evidence for the efficacy of treatment of RSE with anesthetic medications.[2]

Notably, some studies suggest that the use of intravenous anesthetic drugs (IVADs) is associated with negative outcomes.[75,76] Especially pentobarbital has been linked to the development of hypotension requiring prolonged duration of mechanical ventilation and vasopressor therapies,[76] which have in turn been associated with poor long-term outcome.[54] Continuous infusion of thiopental was also associated with more frequent adverse events and worse outcome at 6 months compared to continuous infusions of midazolam.[77] However, it is discussed whether the association with negative outcomes is effectively due to the use of IVADs, or due to confounding by indication, as patients who require continuous infusions are probably more critically ill.[78] A recent prospective two-site cohort study matched 406 patients (139 with IVADs) and found worse outcome in the group receiving IVADs, after adjusting for known outcome predictors.[79] In a review of long-term mortality in relationship to IVADs, the death rate was higher with thiopental/pentobarbital (46%) compared with propofol (36%), midazolam (34%), and ketamine (44%).[80] However, there may be unknown predictors affecting outcome, and therefore additional comparative effectiveness data and randomized controlled trials are needed in this area.

Patients with SRSE are more likely to require multiple medication combinations and prolonged hospitalizations and to present severe deconditioning and often systemic complications. Systemic complications of SE can determine long-term morbidity and mortality, including cardiomyopathy, pulmonary edema, and renal failure.[11,81] It remains unclear how medical treatments affect long-term outcome of SE.

7.3 | Short- and long-term effect of acute treatment of SE

Most literature on the treatment of SE considers short-term endpoints like seizure control or in-hospital mortality. Delays in time to treatment are independently associated with worse outcomes in the short term (higher mortality, higher need for continuous infusions, longer convulsive duration, and more frequent hypotension).[1-3,33,82,83] Families and caregivers play a crucial role, as timely treatment is often possible if families and caregivers administer a rescue medication at home and quickly call emergency services.[84-86] However, a survey of 100 families of patients with epilepsy showed that 87% had a rescue medication prescription, but only 61% of them reported receiving training on how to use it.[86,87] Furthermore, a study showed that only 37.5% of patients received prehospital treatment.[85] Improving these factors could impact short-term outcomes. However, the influence of acute treatment of SE on long-term outcomes appears unclear, and the main predictor of long-term outcome appears to be SE etiology.[53]

8 | LIMITATIONS

Current data need to be interpreted in the setting of often retrospective or unstructured outcome assessment. Additionally, study populations are heterogeneous, different definitions of SE are often applied, and data are acquired in different geographical, socioeconomic, and health care system settings. In addition, follow-up duration and the outcome measures are often variable, reflecting lack of standardized data collection or related guidelines in this field. The current literature does not permit a comparison between results from SE and RSE studies, as they differ in many aspects, including heterogeneity of study populations and study design. Thus far, SE patients are by and large not systematically followed with validated tests repeated over time, or through standardized clinical outcome tools over time. Lastly, we also acknowledge publication bias of specific results, and many publications may suffer from selection and information biases.[80]

9 | OUTLOOK

Long-term outcome after SE encompasses multiple domains including development of subsequent epilepsy, functional and cognitive deficits, and QoL. Mortality remains high, exacerbated by underlying neurological comorbidities, and about one-third of the children develop cognitive sequelae after RSE. Etiology is the main determinant of long-term outcome, but age, treatment timing, and status duration may also play a role, with potential opportunity for care improvements in the latter two. Future studies may either include larger numbers to adjust for confounders or focus on specific etiologies. There is an urgent need for large prospective and multicenter studies, adjusted for confounders and stratified by seizure type, etiology, treatment timing, and age to account for SE heterogeneity, using validated outcome measures, responsive to the intervention. For example, safety studies comparing midazolam, propofol, and barbiturates could be considered, also taking into the account the impact of adverse events caused by prolonged deep sedation[88] and considering electroencephalographic endpoint and duration of anesthetic treatments, such as seizure suppression or burst suppression, and related long-term outcomes. Neuroprotective approaches are likely to improve outcome of patients with acute symptomatic causes, which seems to be one of the most important risk factors.[20] Some studies have demonstrated that functional outcome and likely QoL may improve over time.[15,18,22,23] Promising research in animal models is in the process of identifying biomarkers that can be modulated to minimize long-term functional impairment.[89,90] Additional comparative effectiveness and interventional trials are underway to provide additional data. Translational and clinical research may move these findings to clinical practice in the near future.

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DISCLOSURE OF CONFLICTS OF INTEREST

T.L. serves on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, on the Council (and as President) of the American Clinical Neurophysiology Society, on the American Board of Clinical Neurophysiology, as an Associate Editor for *Seizure*, and as an Associate Editor for *Wyllie's Treatment of Epilepsy*, 6th and 7th editions. He is part of pending patent applications to detect and predict seizures and to diagnose epilepsy. He receives research support from the National Institutes of Health, Epilepsy Research Fund, American Epilepsy Society, Epilepsy Foundation of America, Epilepsy Therapy Project, Patient-Centered Outcomes Research Institute, and Pediatric Epilepsy Research Foundation, and received research grants from Lundbeck, Eisai, Upsher-Smith, Acorda, and Pfizer. He serves as a consultant for Zogenix, Sunovion, Upsher-Smith, Advance Medical, and Lundbeck. He performs video electroencephalogram long-term and intensive care unit 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 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; she performs video-electroencephalographic long-term and intensive care unit monitoring, electroencephalograms, and other electrophysiological studies and bills for these procedures, and she evaluates pediatric neurology patients and bills for clinical care. The authors have no conflicts of interest to report. 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.

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