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Review

# Electrographic seizure burden and outcomes following pediatric status epilepticus

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ABSTRACT

Pediatric status epilepticus carries a substantial risk for morbidity and mortality, but the relationship between seizure burden, treatment, and outcome remains incompletely understood. This review summarizes the evidence linking seizure burden and outcomes among critically ill children in the intensive care unit (ICU), a population in whom accurate quantification of seizure burden is possible using continuous electroencephalographic monitoring. Several high-quality observational studies among critically ill children have reported an association between higher seizure burden and worse outcome, even after adjusting for potential confounders such as age, etiology, and illness severity. Although these studies support the hypothesis that seizures contribute to brain injury and worsen outcome, a causal link between seizures and outcome remains to be proven. The relationship between seizures and outcome is likely complex, and dependent on factors such as etiology, preexisting neurological disability, medication exposure, and possibly individual genetic factors. Studies attempting to define this complex relationship will need to measure and account for these factors in their analyses.

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## 1. Introduction

Convulsive status epilepticus (CSE) is one of the most common childhood neurological emergencies and is associated with significant morbidity and mortality [1,2]. The reported mortality ranges from 2.7 to 5.2% but can be as high as 24–37% in certain parts of the world [3,4]. In a retrospective review of 76 children with CSE that documented a 24% mortality [4], another 58% were left with persistent seizures or new neurological deficits. In a population-based prospective cohort study of 203 CSE survivors, 66% were assessed at a median follow-up of 8.9 years [5], when the cumulative incidence of epilepsy was 24.7%. Motor and intellectual disability were present in 30.6% and 45.5% respectively. Within this cohort [6], 37% of parents reported behavioral issues and 28% of children met criteria for a psychiatric disorder. In summary, children with CSE exhibit a particularly elevated rate of lifetime risk for behavioral and mental health problems beyond the rates associated with non-neurological chronic illnesses [7].

Several studies have described the outcomes of CSE in children in the community and in those presenting to the emergency department, but it is not possible to examine associations between seizure burden and outcomes based on these studies because they did not quantify seizure burden using electroencephalography (EEG). Additionally, in community-based studies of children with status epilepticus, the impact of CSE is difficult to separate from the cumulative effect of longitudinal exposure to seizures over the years. For the purposes of establishing the relationship between seizure burden and outcomes in children, we will be focusing on the population of critically ill children in the intensive care unit (ICU), as within this monitored setting, we are able to quantify seizure burden accurately based on EEG.

## 2. Seizures in critically ill children

Electrographic seizures (ES) and electrographic status epilepticus (ESE) are being increasingly recognized in the pediatric ICU (PICU) [8]. Estimates of seizure prevalence in critically ill children have varied widely, with reports of ES in 10–47% and ESE in 9–32% of critically ill children undergoing continuous EEG (cEEG) monitoring [9–21]. This wide range is likely attributable to heterogeneity in the studied PICU populations as well as the variable indications for cEEG monitoring [22]. Greater awareness of the potentially deleterious effects of seizures and the high seizure prevalence among at-risk patients has led to recommendations for more widespread cEEG monitoring in the PICUs.

Despite the growing evidence that ES and ESE are associated with worse neurological outcomes, the relationship between seizures, brain

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injury, and outcomes is likely complex and remains incompletely understood. This review will use seizures in critically ill children as a model to examine the potentially deleterious effects of seizures, while discussing challenges in quantifying seizure burden, choice, and measurement of outcomes. Finally, we will suggest a framework for evaluating the potential independent contribution of ES and ESE to brain injury and short- as well as long-term outcomes in children.

## 3. Pathophysiological consequences of seizures

In both critically ill adults and children, seizures have been associated with disruptions in neuronal integrity, and the cerebrovascular, electrical, and metabolic milieu of the brain. In critically ill adults, seizures have been linked to glutamate-mediated worsening of cerebral edema [23], long-term ipsilateral hippocampal atrophy [24], transient increases in intracranial pressure [25], and cortical spreading depolarizations [26,27]. Pathological studies support the hypothesis of excitotoxic neuronal injury [28]. Electrographic seizures in adults with severe traumatic brain injury have been associated with significant elevations in the lactate/pyruvate ratio measured by cerebral microdialysis, producing a state of 'metabolic crisis' in the brain [29]. There is similar data from neonates showing impairment in neuronal integrity and energy metabolism associated with seizures. Magnetic resonance spectroscopy (MRS) evidence of increased lactate/choline ratio and diminished N-acetyl aspartate/choline ratio has been associated with clinical seizure severity, even after adjusting for underlying brain injury severity [30]. Also, a 33% decrease in phosphocreatine was noted during seizures when neonates were monitored using P-31 MRS. The phosphocreatine normalized rapidly after antiseizure medications were administered to the neonates [31].

## 4. Quantifying seizure burden

It is widely accepted that the most accurate ascertainment of seizures is by EEG. Electrographic seizures are recognized as rhythmic EEG patterns, often with a spike-and-wave component, evolving in frequency, amplitude, morphology, or spatial extent, with a clear onset and offset [32]. Studies have demonstrated that the interrater agreement for assessing EEG seizures is high [33,34], justifying the quantification of EEG seizures as a research measure. However, it has also become clear that not all seizures are easily distinguished from other rhythmic and periodic EEG patterns (e.g., periodic discharges, rhythmic delta activity) that are frequently encountered in critically ill patients [32]. Furthermore, some types of periodic discharges have also been independently associated with a greater risk for acute seizures and worse outcome [35–37], raising the question of whether periodic discharges alone warrant initiation of antiseizure therapy. Therefore, any study that uses EEG to quantify seizure burden needs to consider how to address subjects who manifest these EEG patterns on the "ictal–interictal continuum" [38].

The alternative to EEG assessment of seizures is the clinical assessment by bedside caregivers. However, the clinical assessment of seizures, even when closely monitored in an ICU setting, is known to lack precision: clinical assessments will fail to recognize nonconvulsive (subclinical or electrographic-only) seizures, which frequently follow convulsive seizures and represent the majority of seizures in critically ill patients. Uncoupling, a phenomenon by which ES persist after clinical seizures have ceased, is common in critically ill patients, especially after administration of antiseizure medications [39,40]. Furthermore, various nonepileptic events (tremors, posturing, etc.) are frequently misclassified as seizures, leading to inappropriate administration of antiseizure medications [41,42]. Therefore, whenever feasible [43], the clinical assessment of seizures in critically ill children should be complemented by EEG.

Accurate quantification of seizure burden is crucial for establishing an association between dose of seizure exposure and outcomes, establishing a potential treatment threshold and measuring the response to treatment. Even though it appears intuitive, quantifying seizure burden using EEG can be challenging. Seizure count is simply the number of seizures, usually expressed per unit time. Seizure duration is the electrographic duration of a seizure from onset to offset. Seizure extent refers to the maximum anatomical extent of seizure involvement, which can either be categorized (e.g., focal, multifocal, hemispheric, bilateral and generalized, or quantified (e.g., number of involved channels in a given EEG montage.

Recent studies have measured the duration of each individual seizure in order to quantify a subject's cumulative and peak seizure burden [20,44]. Seizure burden can be calculated using a sliding time window of fixed duration (e.g., 1 h) (Fig. 1A), or for a series of fixed time periods (e.g., hourly) (Fig. 1B). *Total seizure burden* reflects the cumulative burden of seizures over the entire monitoring period, which may of course vary in peak intensity and spatial extent (Fig. 1B). To account for monitoring periods of varying duration, the total seizure burden can be divided by the duration of monitoring to compute the '*seizure burden proportion*'.

Hourly seizure burden provides a dynamic measure that can be calculated on an ongoing basis in real-time and can, therefore, be used to guide therapy. However, it remains to be determined which of these seizure burden measures correlates best with outcomes. All the above metrics can be further refined by including only seizures with a certain minimum duration (e.g., ≥1 min) or a certain anatomical extent (e.g., categorized as hemispheric or involving 3 or more EEG channels).

Another aspect of seizures that may be relevant for their impact on outcome is the temporal evolution of seizure burden. In neonatal hypoxemic–ischemic encephalopathy [45], distinct patterns of temporal evolution in electrographic seizure burden have been described. Similar patterns are likely to present in other populations, but these temporal profiles (e.g., proximity of seizures to brain injury) remain understudied. A time series representation of hourly seizure burden beginning at the time of brain injury (e.g., Fig.1) would potentially provide the most robust data for establishing which seizure burden metrics in a given population are most closely associated with outcome.

## 5. Outcomes of interest

In a critically ill child, accurate assessment of the impact of seizures and status epilepticus requires selection of an outcome measure that is clinically relevant, practical to administer, and capable of detecting a meaningful change.

Outcome scales such as the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores are easy to score (even by chart review) but are insensitive to subtle changes in behavior, function, and cognition. Recently, there has been a shift toward more comprehensive assessment of clinically relevant neurodevelopmental outcomes using the Griffiths Mental Development Scales, Bayley Scales of Infant Development (BSID), Glasgow Outcome Scale scores (GOS-E Peds), Pediatric Quality of Life (PedsQL), and Vineland Adaptive Behavior Scales (VABS).

Some critically ill children will have substantial preexisting neurobehavioral deficits, necessitating a robust preadmission functional assessment that is usually obtained retrospectively by parent interview. Additionally, to overcome challenges related to transporting patients with complex medical conditions and to maximize follow-up, most large studies have used telephone interviews with a parent or caregiver for performing a detailed follow-up neurobehavioral assessment in lieu of in-person follow-up clinic visits [46]. Of the three commonly used caregiver-reported measures of adaptive behavior, the Vineland Adaptive Behavior Scales-II (VABS-II) [47], the Scales of Independent Behavior-revised [48], and the Adaptive Behavior Assessment System-Second Edition [49], the VABS-II allows for more uniform comparisons throughout the pediatric age range [46]. In addition, in comparison with the other two measures, VABS-II has more items to capture behaviors of very young and low-functioning children.

The timing of assessment is also very important to allow for neurological and functional recovery from the primary etiology as well as critical illness. Most experts consider the 12-month time point as the

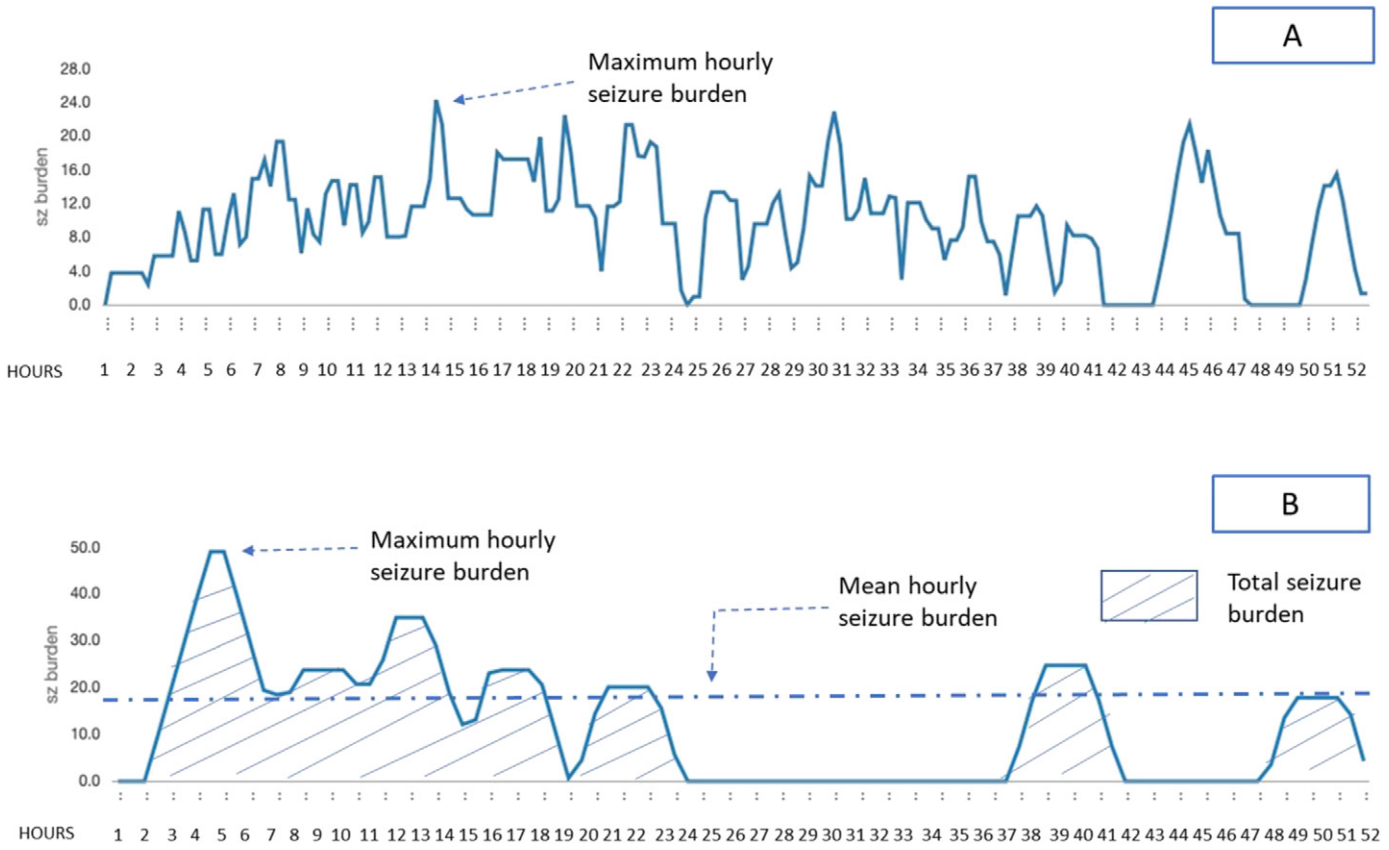


**Fig. 1.** Approaches to quantifying seizure burden. The x-axis represents time, and the y-axis represents hourly seizure burden. A: a 1-hour window is advanced in 1-second increments across the EEG study, resulting in a quasicontinuous measure of hourly seizure burden. B: a 1-hour window is advanced in 1-hour increments across the EEG study, resulting in a less continuous measure of hourly seizure burden, but one for which total seizure burden is represented by the area under the curve.

minimum cutoff for long-term behavioral outcome assessments [46,50]. It is important for the outcome to be assessed by well-trained and experienced interviewers to ensure interrater reliability. Most importantly, the interviewers must be blinded to the child's seizure burden and other clinical details.

Once outcome data are collected, careful consideration needs to be given to determine how they are incorporated into analyses. Utilizing a 'change from preadmission' is problematic for two reasons: firstly, the retrospective assessment of the child's preadmission functional status is subject to recall bias and may lack precision and secondly, children with low preadmission functional status by definition have less opportunity to exhibit functional decline, leading to potential confounding by baseline functional status. The level of analytical granularity can influence statistical power and the likelihood of detecting a change. Quasicontinuous, multicategorical, or dichotomous outcomes each have their unique strengths and weaknesses that should be given careful consideration during study design and power calculation [46].

In summary, practicality, interpretability, reproducibility, and generalizability as well as optimal timing are all important considerations while determining the appropriate outcomes assessment instrument.

## 6. Association between seizure burden and outcomes

Several observational studies have examined short-term and long-term outcomes after ES and ESE in the general population as well as specific subgroups of critically ill children (Tables 1 & 2). Most studies to date have dichotomized seizure burden and utilized a categorical analytical approach classifying burden as ES and ESE, although these definitions vary. Electrographic status epilepticus, defined as a single electrographic seizure lasting more than 30 min or recurrent, independent ES with a cumulative seizure burden proportion of 50% or more, has been consistently associated with higher odds of neurological decline, worse neurocognitive and functional outcomes, longer hospital and PICU stay, and sometimes, a trend toward higher mortality, even after adjusting for age, EEG background, and neurological diagnosis [11,16–18,51,52]. On the other hand, ES that remain below the threshold of status epilepticus are less consistently associated with worse outcome [12,20,21,53]. Hence, when dichotomizing seizure burden as high (ESE) vs. low (ES), a dose–effect relationship between seizure burden and outcomes can be observed.

One study explored the relationship between seizure burden and outcomes utilizing seizure count and duration of seizures as continuous variables. This was a prospective observational study of a combined cohort of 204 comatose neonates and children using 1–3 channel EEG. After demonstrating that the presence of ES was associated with an unfavorable neurological outcome (severe handicap or persistent vegetative state) at 1 month despite adjusting for etiology, age, pediatric index of mortality, Adelaide coma score, and EEG background, the authors further showed that no child had favorable outcomes if they had greater than 139 seizures, if the total duration of ES was greater than 759 min, or if any individual seizure lasted longer than 360 min [21].

To further investigate the relationship between seizure burden and outcome, a prospective observational single-center study of 259 critically ill neonates and children undergoing clinical cEEG monitoring quantified the maximum hourly seizure burden and correlated this with the PCPC score at hospital discharge, adjusting for diagnosis and illness severity. On multivariable analysis, for every 1% increase in maximum hourly seizure burden, the odds of neurological decline increased by 1.13. Furthermore, above a maximum hourly seizure burden threshold of 12 min, there was a marked increase in both the probability and magnitude of neurological decline. These observations of a seizure burden "dose effect" appear to strengthen the case for a causal

**Table 1**
Summary of studies in the general population of critically ill children examining the association between seizure burden and outcomes.

| Author, year | Study population (n) | Measurement of seizure burden | Definition of seizure burden | Outcome assessment | Main findings |
|---|---|---|---|---|---|
| Kirkham et al. [21], 2012 | Children and neonates with coma, n = 204 | Continuous | Number, total duration, and duration of the longest ES | Mortality at discharge and neurological examination at 1-month | ES associated with unfavorable short-term outcomes — severe handicap or vegetative state. |
| Gwer et al. [19], 2012 | Children with coma, n = 82 | Categorical and continuous | **ES** > 6 s; **Clinical SE** > 30 min continuous or >3 seizures/h; Median EEG duration of seizures | Neurological examination at discharge | ES and SE associated with greater risk of poor outcome — death or gross motor deficits at discharge; SE had an even greater risk of poor outcome. |
| Topjian et al. [18], 2013 | Children with acute encephalopathy, n = 200 | Categorical | **ES** > 10s or shorter of associated with a clinical seizure; **ESE**: single >30 min ES or recurrent independent ES with cumulative SB >50% in any 1 h epoch | Mortality and worsening PCPC score from preadmission to discharge | ESE, but not ES, associated with increased mortality risk and PCPC worsening |
| Abend et al. [17], 2013 | Children who underwent ICU EEG monitoring, n = 550 | Categorical | **ES** > 10 s or shorter if associated with a clinical seizure; **ESE**: single ES >30 min or recurrent ES cumulative SB >50% in any 1 h epoch | Mortality and length of stay in the intensive care unit | ESE, but not ES, associated with higher odds of mortality; ESE associated with longer PICU stay |
| Wagenman et al. [55], 2014 | Children with acute neurological condition and encephalopathy, n = 60 | Categorical | **ES** > 10 s or shorter if associated with a clinical seizure; **ESE**: single ES >30 min or recurrent ES cumulative SB >50% in any 1 h epoch | GOS-E Peds, PedsQL, median length of follow-up: 2.7 years | ESE, but not ES, associated with worse long-term functional outcome scores and lower quality of life; ESE associated with increased risk of a subsequent diagnosis of epilepsy |
| Sanchez Fernandez et al. [51], 2014 | Children with convulsive status epilepticus, n = 98 | Categorical | **ES** > 10 s or shorter if associated with a clinical seizure; **ESE**: single ES >30 min or recurrent ES cumulative SB >50% in any 1 h epoch | Length of stay in the intensive care unit | ES associated with longer PICU stay and ESE with even longer PICU stay |
| Payne et al. [20], 2014 | Critically ill children and neonates with an indication for EEG monitoring, n = 259 | Continuous | **ES** > 10 s or shorter if associated with a clinical seizure; **Maximum hourly seizure burden**: maximum percentage of any hour that was occupied by ES **Total seizure burden**: the total amount of time occupied by ES | Neurological decline — worsening PCPC score from preadmission to discharge | Higher probability and magnitude of neurologic decline with SB > 20%; On multivariate analysis, every 1% increase in maximum hourly SB was associated with 1.13 odds of neurological decline. |
| Abend et al. [56], 2015 | Children with acute neurologic condition and encephalopathy, n = 137 | Categorical | **ES** > 10 s or shorter if associated with a clinical seizure; **ESE**: single ES >30 min or recurrent ES cumulative SB >50% in any 1 h epoch | GOS-E Peds, PedsQL, ABAS-II, CBCL, BRIEF, and epilepsy questionnaires; median length of follow-up: 2.6 years | ES and ESE ➔ worse adaptive functioning scores on multivariate analysis; nonsignificant trend to worse scores on behavioral–emotional and executive function scales after ESE |

SB: seizure burden; ES: electrographic seizures; ESE: electrographic status epilepticus; PCPC: Pediatric Cerebral Performance Category; GOS-E Peds: Glasgow Outcome Scale-Extended Pediatric Version; PedsQL: Pediatric Quality of Life Inventory; ABAS-II: Adaptive Behavior Assessment System-II (ABAS-II); CBCL: Child Behavior Checklist; BRIEF: Behavior Rating Inventory of Executive Function.

link between seizures and outcomes and identify an hourly seizure burden threshold of 12 min as a potential therapeutic target [20]. This study also observed that the magnitude of the relationship between seizure burden and outcome appeared to depend on the underlying cause of seizures. Seizures in the context of anoxic brain injury had less influence on the outcome whereas seizures in the context of stroke or meningitis had a greater influence on the outcome [20].

Further work is required to more precisely define these varying relationships between seizure burden and outcome, in order to inform patient-specific decisions on how aggressively to treat ES.

## 7. A causal link between seizure burden and outcome?

There are several challenges in establishing a causal link between seizure burden and outcomes in critically ill children. Although some studies have attempted to adjust for a variety of known confounders, these can be difficult to quantify. Furthermore, the existence of unknown or unmeasurable confounders must also be acknowledged (Fig. 2).

Seizure etiology has long been recognized as an important determinant of both the refractoriness of acute seizures to treatment and long-term outcome. Seizure etiology may directly influence the outcome through a direct brain injury that is independent of seizures (e.g., stroke, hypoxic–ischemic brain injury, traumatic brain injury), or etiology may modify the effects of seizures, or both. Although it may seem attractive to mitigate confounding by etiology by studying subgroups of patients with the same seizure etiology, this may not be practical because etiology is not always known at the time of seizure onset and potential study enrolment, and overly selective enrolment criteria can limit recruitment.

**Table 2**
Summary of studies in specific subgroups of critically ill children examining the association between seizure burden and outcomes.

| Author, year | Study population (n) | Measurement of seizure burden | Definition of seizure burden | Outcome assessment | Main findings |
|---|---|---|---|---|---|
| Bellinger et al. [57], 1999 | Children with D-transposition of great arteries who underwent surgery during infancy, n = 158 | Categorical | Seizures — detected either clinically or by continuous electroencephalography monitoring | Developmental and neurological status at 4 years of age | Perioperative seizures were associated with lower mean Intelligence Quotient scores and increased risk of neurological abnormalities. |
| Gaynor et al. [58], 2006 | Children with congenital heart defects after surgery, n = 178 | Categorical | EEG seizure count and site of origin (frontal and nonfrontal) | BSID II including PDI and MDI at 1 year of age | Postoperative seizure not predictive of a worse neurodevelopmental outcome as assessed by BSID II |
| Bellinger et al. [59], 2009 | Children with D-transposition of great arteries who underwent surgery during infancy, n = 155 | Categorical | Seizures — detected either clinically or by continuous electroencephalography monitoring | Child Behavior Checklist at 4 and 8 years of age; Connors' Parent rating scale at 8 years of age | Postoperative seizures were associated with social and attention problems. |
| Bellinger et al. [53], 2011 | Children with D-transposition of great arteries who underwent surgery during infancy, n = 139 | Categorical | Seizures — detected either clinically or by continuous electroencephalography monitoring | Neuropsychological assessment and brain imaging at 16 years of age | Seizures in the postoperative period were associated with worse outcomes. |
| Arndt et al. [11], 2013 | Children with traumatic brain injury, n = 87 | Categorical | **ES** > 10 s showing evolution in frequency, morphology, & amplitude; **SE**: single seizure >15 min or recurrent seizures >3/h **ESE**: ES + SE | Length of hospital stay and intensive care unit; KOSCHI score at discharge | ESE associated with increased hospital stay but not PICU stay; Worse KOSCHI scores with ES, SE, and ESE |
| Piantino et al. [12], 2013 | Children on extracorporeal life support, n = 19 | Categorical | **ES** > 10 s or shorter if associated with a clinical seizure; **ESE**: single ES >30 min or recurrent ES cumulative SB >50% in any 1 h epoch | Mortality and radiologic evidence of neurological injury | ES associated with MRI abnormalities; No association with increased mortality. |
| Gaynor et al. [60], 2013 | Children with congenital heart defects after surgery, n = 132 | Categorical | EEG seizure count and site of origin (frontal and nonfrontal) | Neurodevelopmental assessment between ages 4 and 5 years | EEG seizure was associated with worse executive function and impaired social interactions/restricted behavior. Seizures were not associated with worse performance for cognition, language, attention, impulsivity, academic achievement, or motor skills. |
| O'Neill et al. [52], 2015 | Children with traumatic brain injury, n = 144 | Categorical | **ES**: paroxysmal discharge that evolved in frequency & location (no duration cutoff) **ESE**: single ES >30 min or recurrent ES with cumulative SB >50% of EEG recording | Mortality, transfer to a rehabilitation facility, length of hospital and intensive care unit stay | Associated with longer hospital stay and ICU stay for both ESE and ES; No association with disposition at ICU discharge. |
| Vaewpanich & Reuter-Rice [16], 2016 | Children with traumatic brain injury, n = 16 | Categorical | **ES** > 10 s **SE**: >30 min continuous | SPNFE and GOS-E Peds at discharge and 4–6 weeks after discharge | Poor outcomes in children with ES and SE |

SB: Seizure burden; ES: Electrographic seizures; ESE: Electrographic status epilepticus; SPNFE: Pediatric speech pathology neurocognitive/functional evaluation; GOS-E Peds: Glasgow Outcome Scale-Extended Pediatric; KOSCHI: Kings Outcome Scale for Childhood Head Injury; BSID II: Bayley Scales of Infant Development II; PDI: Psychomotor Development Index; MDI: Mental Development Index.

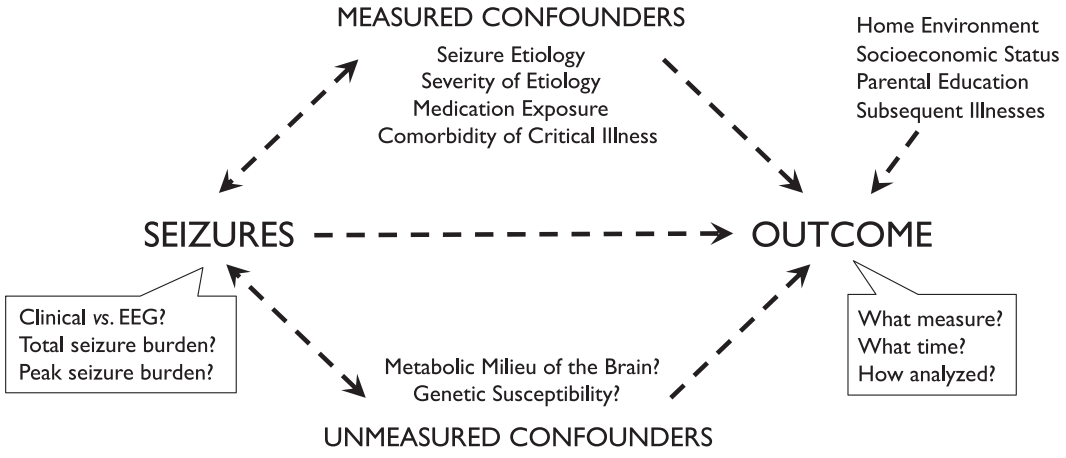


**Fig. 2.** Illustration of potential causal relationships between seizures and outcome.

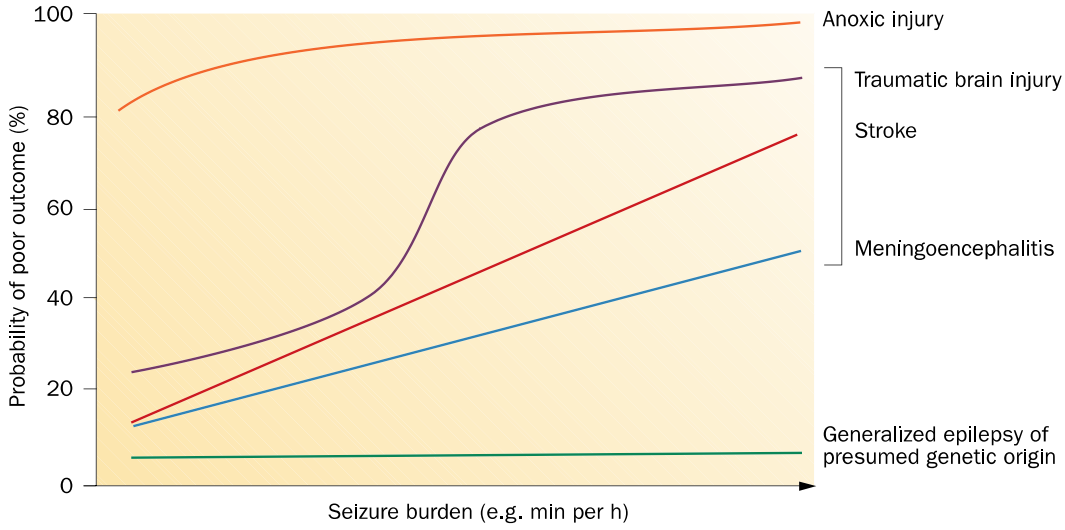


**Fig. 3.** Potential relationships between seizure burden and outcome. Schematic illustration of potential relationships between seizure burden and outcome. The potentially deleterious effects of seizures in the context of acute brain injury are likely to depend on the underlying etiology. The probability of poor outcome might increase linearly or exponentially with increasing seizure burden, or a threshold might exist, above which seizures are harmful.
Reproduced from [54].

Furthermore, even when studying a single etiology, variability in etiology-specific injury severity must still be accounted for (e.g., by neuroimaging measures of infarct volume or traumatic brain injury severity) and factored into analyses of the relationship between seizure burden, treatment, and outcomes. Studies that do include patients with multiple seizure etiologies must either stratify the outcomes analysis by the underlying etiology or apply multivariable regression methods that adjust for confounding and effect-modification by etiology. This will permit the elucidation of potential etiology-specific relationships between seizure burden and outcome (Fig. 3). It is possible that for some diagnoses, the influence of etiology on the outcome will dominate the effects of seizures (e.g., anoxic brain injury) or may mitigate their effects (e.g., epilepsy of presumed genetic origin).

Accounting for baseline neurological status is also of critical importance, because further decline may be difficult to measure among children with preexisting neurological morbidity. Although one strategy is to limit study enrolment to children who are neurologically normal prior to seizure onset, this will limit study recruitment, and also has the drawback of limiting generalizability since many children who experience seizures do have preexisting neurological diagnoses.

Exposure to antiseizure medications may also influence the outcome. Increasing seizure burden is often accompanied by greater use of antiseizure medications such as phenobarbital and phenytoin, which have been shown to have neurotoxic effects in rodent models [61–64]. Furthermore, there is evidence that greater exposure to anesthetic agents during refractory status epilepticus is associated with worse outcome. Therefore, disentangling the potentially deleterious effects of seizures from the potential toxicity due to their treatment remains an important challenge [65–68].

The impact of critical illness per se on cognitive and functional outcomes has been brought to light by recent evidence that cognitive dysfunction is highly prevalent in adult ICU survivors [69]. In critically ill children, neurological and functional morbidity is observed in approximately 30% of PICU survivors, and younger children may be at particular risk. For example, substantial neurologic and functional morbidity has been reported among previously healthy children admitted to the PICU for bronchiolitis [70]. Therefore, illness severity scores such as the Pediatric Risk of Mortality score (PRISM) and the Pediatric Logistic Organ Dysfunction score (PELOD) should be incorporated into any analysis of the relationship between seizure burden and outcome [71,72].

Lastly, there may be a component of individual susceptibility to seizure-induced brain injury in critically ill children. This susceptibility could be determined by a combination of genotype and phenotype as has been shown in preclinical and clinical studies of symptoms and outcomes following concussion [73,74]. Not all such individual factors may be known, and thus, it is likely that in any study, some important confounders will remain unmeasured.

## 8. Conclusions

In summary, several high-quality observational studies have reported an association between higher seizure burden and worse outcome, even after adjusting for potential confounders such as age, etiology, and illness severity. Although these studies support the *hypothesis* that seizures contribute to brain injury and worsen outcome, a causal link between seizures and outcome remains to be proven. The relationship between seizure burden and outcome is likely complex and dependent on factors such as etiology, preexisting neurological disability, medication exposure, and possibly individual genetic factors. Studies attempting to define this complex relationship will need to measure and account for these factors in their analyses.

Although some would argue that a randomized trial of more vs. less aggressive seizure treatment is required to prove causality and, furthermore, establish that more aggressive seizure treatment actually improves outcomes, the ethical and practical barriers to such a trial are considerable. Two randomized controlled trials of EEG-guided vs. clinically guided seizure treatment in neonates with hypoxic–ischemic encephalopathy did not find any differences in outcome between the treatment groups, but both studies were likely underpowered because of challenges with recruitment [75,76]. A potentially more feasible approach would be a multicenter comparative effectiveness study that could harness the often substantial inter- and intrainstitutional variability in the timeliness and intensity of seizure treatment. Such a large observational study would need to recruit a large cohort of critically ill children with seizures (e.g., 500–1000), and carefully account for seizure burden, treatment intensity, and all measurable confounders, in order to provide a more comprehensive understanding of the complex relationship between seizures, their treatment, and outcome.

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## Declaration of competing interest

Cecil Hahn has served as a member of a clinical standardization team for SAGE Therapeutics and as a consultant on clinical trial design to Marinus Pharmaceuticals.

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