Risk Factors Associated with Death in In-Hospital Pediatric Convulsive Status Epilepticus

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

| Citation          | Lodden kemper, Tobias, Tanvir U. Syed, Sriram Ramgopal, Deepak Gulati, Sikawat Thanaviratananich, Sanjeev V. Kothare, Amer Alshekhlee, and Mohamad Z. Koubeissi. 2012. Risk factors associated with death in in-hospital pediatric convulsive status epilepticus. PLoS ONE 7(10): e47474. |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Published Version | doi:10.1371/journal.pone.0047474                                                                                                                                                                                                                             |
| Citable link      | http://nrs.harvard.edu/urn-3:HUL.InstRepos:10510852                                                                                                                                                                                                     |
| Terms of Use      | This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA |
Risk Factors Associated with Death in In-Hospital Pediatric Convulsive Status Epilepticus

Tobias Loddenkemper1,*, Tanvir U. Syed2,3, Sriram Ramgopal1, Deepak Gulati2, Sikawat Thanaviratananich2, Sanjeev V. Kothare1, Amer Alshekhlee3, Mohamad Z. Koubeissi2,4

1 Department of Neurology, Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts, United States of America, 2 Department of Neurology, Case Western Reserve University and University Hospitals, Cleveland, Ohio, United States of America, 3 Department of Neurology, St Louis University, St. Louis, Missouri, United States of America, 4 Department of Neurology, George Washington University, Washington, D.C., United States of America

Abstract

Objective: To evaluate in-patient mortality and predictors of death associated with convulsive status epilepticus (SE) in a large, multi-center, pediatric cohort.

Patients and Methods: We identified our cohort from the KID Inpatient Database for the years 1997, 2000, 2003 and 2006. We queried the database for convulsive SE, associated diagnoses, and for inpatient death. Univariate logistic testing was used to screen for potential risk factors. These risk factors were then entered into a stepwise backwards conditional multivariable logistic regression procedure. P-values less than 0.05 were taken as significant.

Results: We identified 12,365 (5,541 female) patients with convulsive SE aged 0–20 years (mean age 6.2 years, standard deviation 5.5 years, median 5 years) among 14,965,571 pediatric inpatients (0.08%). Of these, 117 died while in the hospital (0.9%). The most frequent additional admission ICD-9 code diagnoses in addition to SE were cerebral palsy, pneumonia, and respiratory failure. Independent risk factors for death in patients with SE, assessed by multivariate calculation, included near drowning (Odds ratio [OR] 43.2; Confidence Interval [CI] 4.4–426.8), hemorrhagic shock (OR 17.83; CI 6.5–49.1), sepsis (OR 10.14; CI 4.0–25.6), massive aspiration (OR 9.1; CI 1.8–47), mechanical ventilation >96 hours (OR 5.6–14.6), transfusion (OR 8.25; CI 4.3–15.8), structural brain lesion (OR 7.0; CI 3.1–16), hypoglycemia (OR 5.8; CI 1.75–19.2), sepsis with liver failure (OR 14.4; CI 5–41.9), and admission in December (OR 3.4; CI 1.6–4.1). African American ethnicity (OR 0.4; CI 0.2–0.8) was associated with a decreased risk of death in SE.

Conclusion: Pediatric convulsive SE occurs in up to 0.08% of pediatric inpatient admissions with a mortality of up to 1%. There appear to be several risk factors that can predict mortality. These may warrant additional monitoring and aggressive management.

Citation: Loddenkemper T, Syed TU, Ramgopal S, Gulati D, Thanaviratananich S, et al. (2012) Risk Factors Associated with Death in In-Hospital Pediatric Convulsive Status Epilepticus. PLoS ONE 7(10): e47474. doi:10.1371/journal.pone.0047474

Received June 14, 2012; Accepted September 12, 2012; Published October 26, 2012

Copyright: © 2012 Loddenkemper et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: TL serves on the Laboratory Accreditation Board for Long Term (Epilepsy and ICU) Monitoring (ABRET), serves as an Associate Editor for Seizure, serves on the American Board of Clinical Neurophysiology, and on the Council of the American Clinical Neurophysiology Society, performs Video EEG longterm monitoring, EEGs, and other electrophysiological studies at Children's Hospital Boston and bills for these procedures (20%), receives support from National Institutes of Health (NHLI)/National Institute of Neurological Disorders and Stroke (NINDS) 1R21NS076892-01 (2011-2013), is supported by a Career Development Fellowship Award from Harvard Medical School and Children's Hospital Boston, by the Program for Quality and Safety at Children's Hospital Boston, from the Payer Provider Quality Initiative, the Translational Research Project at Children's Hospital Boston, receives funding from the Epilepsy Foundation of America (EF-213563 & EF-213882), and from the Center for Integration of Medicine & Innovative Technology (CIMIT/DOD), and received investigator initiated research support from Eisai and Lundbeck, Dr. TS, SR, DG, and ST have nothing to disclose. Dr. SK performs Video EEG longterm monitoring, EEGs, and other electrophysiological studies at Children's Hospital Boston and bills for these procedures, is interim medical director of the Center for Pediatric Sleep Disorders at Children's Hospital Boston, and has received research support from National Institute of Health (1 R1C HL099749-01 (R21) (2009-12), and RFA-HL-09-001 (2010-14) and the Harvard Catalyst (2010-11). He also serves on the editorial board of the journal Pediatric Neurology. Dr. AA has nothing to disclose. Dr. MK has no conflict of interest related to the current work, has received grant support from the Coulter Foundation, and is on the Speakers' Bureau of UCB and Pfizer. There are no patents, products in development or marketed products to declare. This does not alter the authors’ adherence to all the PLOS ONE policies on sharing data and materials.

* E-mail: Sriram.ramgopal@childrens.harvard.edu

† These authors contributed equally to this work.
Introduction

Status epilepticus (SE) is characterized by prolonged seizures or by multiple seizures without full restoration of consciousness between events [1]. The condition is associated with significant morbidity and mortality. SE is thought to have a fatality rate of approximately 2% [2,3]. Complications of SE are also significant and include refractory epilepsy, neurologic deficits and repeated episodes of SE [4].

While a number of studies have identified associations for poor outcomes in SE [5,6], the use of publicly available hospital databases with large sample sizes may allow for better determination of morbidity and mortality risk factors for patients with this condition. In this study, we investigate potential risk factors leading to death in children presenting with generalized convulsive SE.

Patients and Methods

Study Population

This study utilized patient data acquired from the Kids’ Inpatient Database (KID). The KID dataset has been set up through the Healthcare Cost and Utilization Project (HCUP) and is the only all-payer inpatient care database for children in the United States. Data from both insured and uninsured pediatric patients, defined as individuals less than 20 years of age, are collected. Data collected from KID include demographic information, including patient age, gender, race, median income and ZIP code, primary and secondary diagnoses, procedures, payment information, and patient length of stay. KID also collects information on factors including hospital size, teaching status, type of hospital and hospital location. We used data from the years 1997, 2000, 2003 and 2006. The 1997 database includes data from 2,521 hospitals in 22 states, the 2000 database includes data from 2,784 hospitals in 27 states, the 2003 database includes data from 3,438 hospitals in 36 states, and the 2006 database includes data from 3,739 hospitals in 38 states. Twenty percent of normal newborn births and 80% of the inpatient admissions from each institution are included in the dataset as a systematic random sample [7].

Standard Protocol Approvals

Prior to data analysis, the Institutional Review Boards of Case Western Reserve University and University Hospitals, Cleveland, OH, and Boston Children’s Hospital, Boston, MA, granted exempt status to this study. Informed consent was not required. This study was done in accordance with the HCUP user agreement.

Data Acquisition

We queried KID for cases with a diagnostic code of generalized convulsive status epilepticus via usage of the International Statistical Classification of Diseases and Related Health Problems, 9th revision (ICD-9) code 345.3. This code corresponds to “grand mal status”. No other ICD-9 codes were used. Data pertaining to month of admission, admission source (from the emergency room, at birth, from outside the hospital and from outside the facility), sex, elective admission or not, age, length of stay, ethnicity, income level (assessed as median income per ZIP code), hospital type (general hospital, children’s hospital, or general hospital with a children’s unit), hospital bed size, hospital location (rural versus urban and geographic region), and teaching status of hospital were collected. We also used ICD-9 codes to collect data pertaining to patient comorbidities, interventions and complications (table 1).

Outcomes pertaining to mortality, which were listed separately in the KID dataset, were collected for each patient.

Statistical Analysis

Univariate logistic testing was used to screen for significant risk factors of death. Risk factors with an associated p-value less than 0.20 were entered into a stepwise backwards conditional multivariable logistic regression procedure. The multivariable model only retained risk factors with an associated p-value less than 0.05. Two-way interaction terms were entered one at a time into the resulting multivariable model and were retained if the associated p-value was less than 0.05. Model validity was assessed using the Hosmer and Lemeshow goodness-of-fit test with p-value greater than 0.05 indicating adequate model fit of data. All statistical analyses were performed in Stata 11.0 (Statacorp, College Station, TX).

Results

Description of Patient Population and Mortality Rate

A total of 14,965,571 patients were included based on the KID datasets from 1997, 2000, 2003 and 2006. Of these, 12,365 patients (0.083%) were diagnosed with convulsive SE, including 5,541 (44.8%) girls. Five patients (<0.0001%) were excluded from the study due to insufficient data for the tested variables. Mean patient age was 6.2±5.3 years (range <1–20 years, median 5 years). One-hundred-and-seventeen patients (0.95%) with convulsive SE died during their inpatient admission. Additional demographic data are provided in table 2.

Risk Factor Analysis

Logistic testing was done to identify potential risk factors for death in convulsive status epilepticus, and those risk factors associated with a p-value of 0.20 were entered into a multivariate model. Factors with a p-value of less than 0.05 were taken as significant following model verification. Univariate and multivariate calculations are provided in tables 1, 3 and 4.

Risk Factors Based on Demographic Data

African American children were at a significantly lower risk of mortality following an episode of convulsive SE (p = 0.009). Patients in other racial groups did not have an associated increase or decrease in mortality. No association was found between patient age and mortality risk. Household income, calculated as the average income in a ZIP code region, was also not a significant risk factor for death.

Risk Factors Based on Hospital Admission

Using univariate analysis, cases referred from outside hospitals were associated with a higher rate of mortality, as were Children’s Hospitals, Teaching Hospitals, and General Hospitals with a Children’s Unit. These findings were not significant in multivariate analysis. Patient length of stay, weekend versus weekday admission, hospital size and geographic region of hospital were not associated with an increased risk of mortality. None of these factors emerged as significant in multivariate analysis.

Risk Factors Based on Comorbidities

A number of patient comorbidities corresponded to a greater mortality risk in convulsive SE. Sepsis (p<0.001), hypoglycemia (p = 0.004), near-drowning episode (p = 0.001), hemorrhagic shock (p<0.001), structural brain lesions (p<0.001), massive aspiration (p = 0.008), and postoperative sepsis with liver failure (p<0.001)
### Table 1. Univariate calculations of complications and comorbidities from the KID database.

| Predictor                        | ICD-9 Code                  | Total N | Predictor N | OR       | Lower 95% | Upper 95% | P        |
|----------------------------------|-----------------------------|---------|-------------|----------|-----------|-----------|----------|
| **Metabolic**                    |                             |         |             |          |           |           |          |
| Hyponatremia                     | 276.1                       | 12360   | 238         | 3.31     | 1.52      | 7.18      | 0.002    |
| Hypoxia                          | 799.0, 770.8, 768, 348.1,   | 12360   | 293         | 12.35    | 8.01      | 19.04     | <.001    |
|                                  | 768.5, 768.6, 768.9         |         |             |          |           |           |          |
| Drug overdose                    | 966                         | 12360   | 12          | -        | -         | -         |          |
| Hepatic encephalopathy          | 572.2                       | 12360   | <10         | -        | -         | -         |          |
| Metabolic derangements          | 277, 348.31                 | 12360   | 105         | 4.26     | 1.54      | 11.76     | 0.005    |
| Severe malnutrition             | 260, 261, 262, 263          | 12360   | 60          | 3.65     | 0.88      | 15.14     | 0.074    |
| Toxic                            | 349.82, 323.7, 983, 984,    | 12360   | 19          | -        | -         | -         |          |
|                                  | 985, 988, 989               |         |             |          |           |           |          |
| Hypoglycemia                     | 250.8, 251.0, 251.1, 251.2,| 12360   | 67          | 8.77     | 3.46      | 22.23     | <.001    |
|                                  | 300.19, 775.6               |         |             |          |           |           |          |
| Drug withdrawal                  | 292.0, 779.5                | 12360   | <10         | -        | -         | -         |          |
| **Infectious**                   |                             |         |             |          |           |           |          |
| Sepsis                           | 038, 771.8, 995.91, 995.92,| 12360   | 44          | 33.56    | 16.17     | 69.66     | <.001    |
|                                  | 771.81                      |         |             |          |           |           |          |
| Cerebral malaria                 | 084.9                       | 12365   | <10         | -        | -         | -         |          |
| Disseminated tuberculosis        | 018                         |         | -           | -        | -         | -         |          |
| Acute viral encephalitis        | 049.9, 062, 064, 139.0,     | 12360   | 34          | 10.37    | 3.12      | 34.40     | <.001    |
|                                  | 323.0, 323.01               |         |             |          |           |           |          |
| Central nervous system infections| V12.42                      | 12365   | <10         | -        | -         | -         |          |
| Meningoencephalitis             | 323.0, 323.4                | 12360   | <10         | -        | -         | -         |          |
| Bacterial meningitis            | 320, 320.7, 320.8, 320.81, | 12360   | <10         | -        | -         | -         |          |
|                                  | 320.82, 320.9               |         |             |          |           |           |          |
| Infectious encephalopathy       | 136.9, 323.5, 323.9, 348.3  | 12360   | 394         | 2.57     | 1.29      | 5.10      | <.007    |
| Severe malaria                   | 084, 084.9, 084.4, 084.5,   | 12330   | -           | -        | -         | -         |          |
|                                  | 084.6, 084.7, 084.8         |         |             |          |           |           |          |
| Pneumonia                        | 480, 480.8, 489.0, 481,     | 12360   | 51          | 6.69     | 2.05      | 21.78     | 0.002    |
|                                  | 482, 482.8, 483, 485, 011.6 |         |             |          |           |           |          |
| Meningitis                       | 013.0, 036.0, 320, 047.8,   | 12360   | 44          | -        | -         | -         |          |
|                                  | 047.9, 320.1, 321, 320.8,  |         |             |          |           |           |          |
|                                  | 322                          |         |             |          |           |           |          |
| Bacteremia                       | 790.7, 771.83               | 12360   | 58          | -        | -         | -         |          |
| Viral encephalitis               | 062, 063, 064, 139.0, 323.0,| 12360   | 34          | 10.37    | 3.12      | 34.39     | <.001    |
|                                  | 049.9                        |         |             |          |           |           |          |
| RSV infection                    | 079.6                        | 12360   | 42          | 2.57     | 0.35      | 18.81     | 0.354    |
| Postoperative sepsis and liver failure | 998.59                    | 12360   | 26          | 59.93    | 26.14     | 137.42    | <.001    |
| Septic shock                     | 785.52, 785.59               | 12360   | 46          | 57.93    | 30.35     | 110.59    | <.001    |
| **Hemodynamic**                 |                             |         |             |          |           |           |          |
| Congenital heart disease        | 746.9                        | 12360   | <10         | -        | -         | -         |          |
| Hypotension                      | 458, 458.0, 458.1, 458.2,   | 12360   | 146         | 15.96    | 9.28      | 27.47     | <.001    |
|                                  | 458.29, 458.8, 458.9         |         |             |          |           |           |          |
| Intractable hypertension        | 401, 403, 403.0, 405, 405.0 | 12360   | 104         | 5.48     | 2.19      | 13.71     | <.001    |
| Cardiac failure                  | 428.9                        | 12360   | <10         | -        | -         | -         |          |
| Hemorrhagic shock                | 785.59, 958.4               | 12360   | 29          | 50.93    | 22.67     | 114.39    | <.001    |
| Post cardiac arrest              | 997.1                        | 12360   | <10         | -        | -         | -         |          |
| **Neurologic**                  |                             |         |             |          |           |           |          |
| Cerebral palsy                   | 333.71, 343, 343.0, 343.1,  | 12360   | 2132        | 0.64     | 0.37      | 1.12      | 0.118    |
|                                  | 343.2, 343.3, 343.8, 343.9  |         |             |          |           |           |          |
| Subdural Hematoma                | 432.1, 767.0                | 12360   | 21          | 11.19    | 2.58      | 48.59     | <.0001   |
| Cerebrovascular accident         | 434.01, 434.11, 434.91      | 12360   | 36          | 37.07    | 17.32     | 82.07     | <.007    |
| Brain trauma                     | 850, 767.0, 850.9 854, 310.2| 12360   | 14          | -        | -         | -         |          |
| Acute cerebrovascular disease    | 436, 437, 437.1, 437.8,     | 12360   | 46          | 2.34     | 0.32      | 17.10     | 0.403    |
|                                  | 437.9 438, 438.8, 438.9     |         |             |          |           |           |          |
were associated with increased mortality. Though risk factors such as hypertension, subdural hemorrhage, viral encephalitis, and infectious encephalopathy were significant risk factors in univariate analysis, they did not emerge as significant factors following multivariate calculations. Other comorbidities, including a previous diagnosis of epilepsy, antiepileptic medication withdrawal, fever, esophageal tears, post-cardiac arrest status, brainstem tumors, infantile spasms, other encephalitis, and hydrocephalus were not associated with increased mortality.

### Risk Factors Based on Procedures

The need for blood transfusion was associated with greater risk of death \( p < 0.001 \). While intubation was not a risk factor for death, mechanical ventilation for more than 96 hours was associated with a higher mortality \( p < 0.001 \). Ventriculoperitoneal shunt placement was not associated with higher mortality.

### Discussion

#### Summary

This retrospective study utilized the KID dataset to identify a number of risk factors for poor outcome in pediatric patients diagnosed with convulsive status epilepticus. Higher risk was associated with end-of-year hospital admissions, various patient-related comorbidities, blood transfusion and prolonged mechanical ventilation. African American ethnicity was associated with a lower risk of mortality. A review of the literature is presented in table 5.

#### Mortality rate

The mortality rates of convulsive SE in previous studies vary. Some studies report a less than 2% mortality \([2,3]\) whereas other studies provide figures over 30% \([8]\). The mortality rate of convulsive SE in our study was approximately 1%. This finding corresponds to mortality rates from previous research. A statewide study based in California utilized a dataset including over

---

**Table 1. Cont.**

| Predictor                          | ICD-9 Code | Total N | Predictor N | OR   | Lower 95% | Upper 95% | P    |
|-----------------------------------|------------|---------|-------------|------|-----------|-----------|------|
| Brain death                       | 348.8      | 12360   | 119         | 9.19 | 4.54      | 18.61     | <.001|
| Brainstem tumor                   | 191.7, 225.9 | 12360   | <10         | -    | -         | -         | -    |
| Structural brain lesion           | 348.8      | 12360   | 119         | 9.19 | 4.54      | 18.61     | <.001|
| Intracranial hemorrhage           | 800.3, 800.8 | 12360   | <10         | -    | -         | -         | -    |
| Brainstem hemiation               | 348.4      | 12360   | 33          | 24.46| 9.90      | 60.40     | <.001|
| Epilepsy                          | 345        | 12360   | 376         | 0.84 | 0.26      | 2.65      | 0.763|
| Generalized Convulsive Epilepsy   | 345.1      | 12360   | 38          | -    | -         | -         | -    |
| Generalized Non-Convulsive Epilepsy| 345.0      | 12360   | 19          | -    | -         | -         | -    |
| Infantile spasms                 | 345.6      | 12360   | <10         | -    | -         | -         | -    |
| Hydrocephalus                     | 331        | 12360   | 832         | 0.62 | 0.25      | 1.51      | 0.291|
| Obstructive hydrocephalus         | 331.4      | 12360   | 472         | 0.89 | 0.33      | 2.42      | 0.821|
| Communicating hydrocephalus       | 331.3      | 12360   | 16          | -    | -         | -         | -    |
| Idiopathic hydrocephalus          | 331.5      | 12360   | <10         | -    | -         | -         | -    |
| Congenital hydrocephalus          | 742.3      | 12360   | 349         | 0.30 | 0.04      | 2.12      | 0.224|
| CNS Malformation in fetus         | 655.0      | 12360   | <10         | -    | -         | -         | -    |
| Tuberous sclerosis                | 759.5      | 12360   | 124         | 0.85 | 0.12      | 6.13      | 0.871|
| Rasmussen encephalitis            | 323.81     | 12360   | <10         | -    | -         | -         | -    |

**Other**

| Predictor                          | ICD-9 Code | Total N | Predictor N | OR   | Lower 95% | Upper 95% | P    |
|-----------------------------------|------------|---------|-------------|------|-----------|-----------|------|
| Non compliance                    | V15.81     | 12360   | <10         | -    | -         | -         | -    |
| Near drowning                     | 994.1      | 12360   | <10         | 26.38| 2.93      | 237.80    | 0.004|
| Congenital malformations          | V13.6, V13.69 | 12360   | <10         | -    | -         | -         | -    |
| Massive aspiration                | 507, 770.1, 770.18, E879.4 | 12360   | 711         | 2.25 | 1.28      | 3.96      | 0.005|
| Esophageal tear                   | 530.89     | 12360   | <10         | -    | -         | -         | -    |
| Fever                             | 780.6      | 12360   | 612         | 1.04 | 0.45      | 2.37      | 0.929|

**Interventions**

| Predictor                          | ICD-9 Code | Total N | Predictor N | OR   | Lower 95% | Upper 95% | P    |
|-----------------------------------|------------|---------|-------------|------|-----------|-----------|------|
| Transfusion                       | 99.01–99.09 | 12360   | 110         | 36.48| 22.21     | 59.93     | <.001|
| Ventriculoperitoneal shunt        | 2.31–2.39  | 12360   | 23          | 4.79 | 0.64      | 35.82     | 0.127|
| Intubation                        | 96.04      | 12360   | 19          | -    | -         | -         | -    |
| Mechanical ventilation            | 96.71      | 12360   | 3351        | 12.64| 7.87      | 20.30     | <.001|
| Mechanical ventilation 96 hours   | 96.72      | 12360   | 426         | 22.74| 15.53     | 33.30     | <.001|

ICD-9 – International Classification of Disease, 9th edition, RSV – respiratory syncytial virus.
doi:10.1371/journal.pone.0047474.t001
19,000 adults and children admitted for SE and found an in-hospital mortality rate of 1.9% [3]. A prospective study evaluating intractable epilepsy in 613 children found a death rate of 1.6% over 4 years [9]. Another prospective study found a mortality rate of 2% in 47 pediatric patients with SE [10]. Studies with higher mortality rates may have analyzed high-risk subgroups, such as SE patients with pediatric intensive care unit (ICU) admissions [8] or cases of refractory SE only [11]. Because prolonged seizures are thought to be a risk factor for complications and death, studies that maintained criteria of a minimum seizure length of 30 or more minutes may have subsequently reported higher fatality rates [12,13]. Investigators who studied mortality over months to years of follow-up reported higher fatality rates [12]. Most studies of SE do not specifically investigate pediatric patients. Because the mortality of SE may rise with age [5,14], the inclusion of adult patients can result in a higher case-fatality rate. However, the age-specific incidence of epilepsy is highest in infancy and early childhood and decreases progressively as children grow up [15].

Demographic data

Race. Children of African American ethnicity were found to have lower mortality rates in convulsive SE compared to children of other ethnic groups. In a retrospective study analyzing risk factors for mortality in status epilepticus in Richmond, Virginia, African American ethnicity was found to correlate with decreased mortality risk in univariate, though not multivariate, analysis [14]. While they may have decreased risk of mortality compared to other racial groups, African American children have also been noted to present in SE disproportionately more frequently [3,16]. Because decreased mortality in status persisted in spite of consideration of socioeconomic factors, a heritable resistance to seizure-related mortality in this population cannot be ruled out.

Sex. The importance of gender in the risk assessment of SE is debated. While some studies have identified that males are more likely to present in status [17], other studies have found the opposite [18]. Mortality outcomes in status epilepticus between males and females are similarly conflicting [3,5,6]. While our study found that more males presented in SE than females, we did not find sex to be a significant risk factor in predicting mortality outcomes.

Age. Some studies have found an association between SE mortality and children of younger ages [19], whereas others have noted that older patients have a higher risk of death during SE [5,14]. SE is also noted to occur more frequently in younger patients [5]. Age was not found to be a significant independent risk factor for death in our study.

Hospital Data

Time of Year. We tested each month individually as a predictor of mortality and subsequently tested statistically significant months in the multivariable mortality model to account for potential seasonal variations in disease severity, as may occur with infectious or epidemic disease processes. Hospital admissions for convulsive SE during the month of December were associated with an increased risk of mortality. More research will be needed to verify these data and to identify possible causes. Seasonal variations in infections such as bacterial meningitis [20] and viral encephalitis [21] and other respiratory tract infections may have played a role in this annual variation.

Teaching and Children’s Hospitals. The univariate analysis identified a significant association between deaths and admission into Teaching Hospitals, Children’s Hospitals and General Hospitals with a Children’s unit. In addition, referrals from outside hospitals are also associated with significant mortality. None of these factors emerged as significant in the multivariate analysis. We believe that some of these findings may be related to referral bias, as more severe cases of SE are likely to be referred to Children’s Hospitals and teaching institutions.

Comorbidities

Symptomatic epilepsy. Structural brain lesions, as demonstrated by imaging or autopsy findings, emerged as a risk factor for death in our study. This finding is in concordance with results from previous studies suggesting higher mortality in convulsive SE patients with structural lesions, such as brain tumors [6], cerebral dysgenesis [12,22], neurodegenerative disease [6], cerebral palsy [12] or other brain malformations [19]. Mortality may be higher in patients with acute symptomatic SE and neurological injury [23].

Pulmonary complications. Aspiration was a common comorbid condition associated with death in pediatric patients.
Table 3. Univariate calculations of hospital and demographic data from the KID database.

| Predictor                     | Total N | Predictor N | OR  | Lower 95% | Upper 95% | P    |
|-------------------------------|---------|-------------|-----|-----------|-----------|------|
| January Admission             | 12360   | 957         | 1.00| -         | -         | -    |
| February Admission            | 12360   | 983         | 1.95| 0.67      | 5.74      | 0.22 |
| March Admission               | 12360   | 992         | 2.13| 0.74      | 6.16      | 0.16 |
| April Admission               | 12360   | 878         | 1.97| 0.66      | 5.90      | 0.23 |
| May Admission                 | 12360   | 963         | 1.59| 0.52      | 4.89      | 0.42 |
| June Admission                | 12360   | 934         | 1.85| 0.74      | 5.54      | 0.27 |
| July Admission                | 12360   | 935         | 1.44| 0.45      | 4.54      | 0.54 |
| August Admission              | 12360   | 899         | 2.14| 0.73      | 6.28      | 0.17 |
| September Admission           | 12360   | 883         | 1.08| 0.31      | 3.75      | 0.90 |
| October Admission             | 12360   | 999         | 1.73| 0.58      | 5.18      | 0.33 |
| November Admission            | 12360   | 963         | 0.99| 0.29      | 3.44      | 0.99 |
| December Admission            | 12360   | 1042        | 4.11| 1.55      | 10.89     | 0.01 |
| Admission Source              | 121999  |             |     |           |           |      |
| Emergency room                | 7674    | 1.00        | -   | -         | -         | -    |
| Birth                         | 2197    | 1.53        | 0.94| 2.48      | 0.084     |      |
| Outside Hospital              | 2042    | 2.07        | 1.32| 3.23      | 0.001     |      |
| Outside Facility              | 286     | 2.46        | 0.98| 6.21      | 0.055     |      |
| Weekend Admission             | 12146   | 3389        | 1.36| 0.93      | 2.00      | 0.114|
| Female                        | 12360   | 5537        | 1.17| 0.81      | 1.69      | 0.392|
| Elective Admission            | 11333   | 738         | 1.34| 0.67      | 2.66      | 0.48 |
| Age in years (if more than 1 year old) | 12319 | -           | 1.03| 0.99      | 1.06      | 0.108|
| Age in Days (if less than 1 year old) | 801  | -           | 1.00| 0.99      | 1.00      | 0.327|
| Length of Stay                | 12360   | -           | 1.03| 1.02      | 1.04      | <0.001|
| Race                          | 12360   |             |     |           |           |      |
| White                         | 4697    | 1.00        | -   | -         | -         | -    |
| Black                         | 1943    | 0.49        | 0.24| 1.01      | 0.053     |      |
| Hispanic                      | 2044    | 0.78        | 0.43| 1.41      | 0.412     |      |
| Other                         | 3676    | 1.43        | 0.95| 2.15      | 0.088     |      |
| Urban/Rural by ZIP Code       | 7506    |             |     |           |           |      |
| Large                         | 4306    | 1.00        | -   | -         | -         | -    |
| Small                         | 2187    | 1.27        | 0.76| 2.10      | 0.361     |      |
| Metropolitan                  | 638     | 1.21        | 0.54| 2.73      | 0.639     |      |
| Non-core                      | 375     | 1.18        | 0.42| 3.32      | 0.754     |      |
| Income per ZIP Code           | 12006   |             |     |           |           |      |
| 1st quartile                  | 3076    | 1.00        | -   | -         | -         | -    |
| 2nd quartile                  | 3133    | 1.11        | 0.64| 1.92      | 0.722     |      |
| 3rd quartile                  | 2776    | 1.53        | 0.90| 2.59      | 0.115     |      |
| 4th quartile                  | 3012    | 1.28        | 0.74| 2.19      | 0.376     |      |
| Hospital Type                 | 11693   |             |     |           |           |      |
| General                       | 4897    | 1.00        | -   | -         | -         | -    |
| General with children's unit  | 4125    | 1.60        | 1.01| 2.54      | 0.045     |      |
| Children's                    | 2671    | 2.14        | 1.32| 3.44      | 0.002     |      |
| Hospital Bed Size             | 11936   |             |     |           |           |      |
| Small                         | 1696    | 1.00        | -   | -         | -         | -    |
| Medium                        | 3430    | 1.20        | 0.64| 2.25      | 0.563     |      |
| Large                         | 6810    | 1.16        | 0.65| 2.07      | 0.62      |      |
| Urban Hospital                | 11936   | 11265       | 3.33| 0.82      | 13.51     | 0.092|
| Hospital Region               | 12360   |             |     |           |           |      |
| Northeast                     | 2528    | 1.00        | -   | -         | -         | -    |
with convulsive SE. The risk of aspiration was specifically found to be an independent risk factor for mortality in our study. Pneumonia was identified as a cause of death in a prior retrospective pediatric study [22], a pediatric prospective study [24], and in a pediatric drug trial for management of status epilepticus [25]. In our population it is unclear how many cases of pneumonia were causes or consequences of SE.

**Sepsis and hemodynamic compromise.** Sepsis emerged as an important risk factor for death in our pediatric population. Sepsis may occur as a consequence of pneumonia or from other infective foci. A retrospective study on pediatric ICU patients identified sepsis to be a major cause of death in children with prolonged (>45 minute) episodes of SE [8]. Another study on emergency management procedures in children presenting with SE also identified sepsis as a risk factor for death [26]. Infections may also be an important cause of SE, particularly in cases that were presumably induced by febrile illness or pneumonia [27]. Our study also identified postoperative sepsis with liver failure to be significant enough to constitute an independent risk factor, and this finding is also backed by a previous pediatric case series [28] and by another series on refractory pediatric SE [4]. Hemorrhagic shock was identified as a risk factor for death. In a trial comparing the use of phenytoin and midazolam in school-age children, hemorrhagic shock was noted as a cause of death [25].

**Metabolic complications.** Hypoglycemia emerged as an independent risk factor for death in pediatric convulsive SE. Hypoglycemia increased the risk of neurological sequelae in a prospective study in children [29]. Hypoglycemia may also be a cause of SE [10,16]. Metabolic complications were associated with an increased risk of mortality using univariate analysis. Previous work has noted similar findings [25] and has more specifically associated deaths to hyponatremia [26]. Liver dysfunction, as mentioned above, is another potential source of metabolic dysfunction.

**Near drowning.** Convulsive SE related to near-drowning episodes constituted an independent risk factor for mortality in our series and other studies [30]. Near-drowning episodes may occur as a consequence of seizures [31]. Conversely, SE may also occur as a result of cerebral anoxia following such an event [32].

**Intracranial infections.** The importance of brain infections in leading to SE or resulting in mortality has been noted in previous studies. A prospective pediatric study identified meningitis and encephalitis as causes of SE. Meningitis was also an

| Table 3. Cont. |
|----------------|
| Predictor      | Total N | Predictor N | OR   | Lower 95% | Upper 95% | P     |
|----------------|---------|-------------|------|-----------|-----------|-------|
| Midwest        | 2488    | 1.39        | 0.77 | 2.53      | 0.273     |       |
| South          | 4125    | 1.13        | 0.65 | 1.98      | 0.669     |       |
| West           | 3219    | 1.54        | 0.88 | 2.68      | 0.13      |       |
| Teaching Hospital | 11936  | 9156        | 2.16 | 1.23      | 3.79      | 0.007 |

| Table 4. Significant risk factors for death in pediatric patients with convulsive status epilepticus following multivariate analysis. |
|----------------------------------------------------------------------------------------------------------------------------------|
| Predictor                                      | Odds Ratio | P Value | Lower 95% | Upper 95% |
| African American Race                          | 0.36       | 0.009   | 0.17      | 0.78      |
| December Admission                             | 3.38       | <0.001  | 2.01      | 5.67      |
| Admission Source                               |            |         |          |           |
| Emergency Room                                 | 1.00       | -       | -        | -        |
| Birth                                          | 1.34       | 0.279   | 0.79     | 2.29     |
| Outside Hospital                               | 1.58       | 0.073   | 0.96     | 2.60     |
| Outside Facility                               | 2.05       | 0.159   | 0.75     | 5.56     |
| Comorbidities                                  |            |         |          |           |
| Sepsis                                         | 10.14      | <0.001  | 4.02     | 25.57    |
| Hypoglycemia                                   | 5.79       | 0.004   | 1.75     | 19.16    |
| Near Drowning                                  | 43.17      | 0.001   | 4.37     | 426.82   |
| Hemorrhagic Shock                              | 17.83      | 0.001   | 6.47     | 49.12    |
| Structural Brain Lesion                        | 7.01       | <0.001  | 3.07     | 15.98    |
| Massive Aspiration                             | 9.11       | 0.008   | 1.77     | 47.01    |
| Postoperative Sepsis with Liver Failure         | 14.44      | <0.001  | 4.98     | 41.86    |
| Procedures                                     |            |         |          |           |
| Transfusion                                    | 8.25       | <0.001  | 4.32     | 15.78    |
| Mechanical Ventilation                         | 9.03       | <0.001  | 5.59     | 14.60    |
| >72 hours                                      |            |         |          |           |

doi:10.1371/journal.pone.0047474.t003

doi:10.1371/journal.pone.0047474.t004
Table 5. Selected historical studies of status epilepticus with salient findings.

| Author, Year and Study Design | Follow up | Mortality rate | Predictors/Risk Factors |
|-------------------------------|-----------|----------------|-------------------------|
| Aicardi et al, 1970 [12]      | Discharge Unclear | 4.2% (10/239) 11% (27/239) | Prolonged SE, cerebral disease |
| Chevrie et al, 1978 [19]      | <4 year f/u | 21/334 in 1st year | Symptomatic seizures, age <6 months |
| Dunn et al, 1988 [13]         | Discharge | 8.24% (8/97) | Severe pre-existing brain damage, meningitis and encephalopathy |
| Maytal et al, 1989 [41]       | 13.2 months | 7.2% (7/97) | Prolonged SE |
| DeLorenzo et al, 1992 [14]    | 7 years | 2.3% of children 25% in adults | Tumor, hematological disease, anoxia, metabolic and congenital malformations |
| Scholtes et al, 1996 [42]     | Discharge | 11.5% (13/112) | Anoxia, presence of >1 complication, insufficient therapy, prolonged duration (>8 hrs) |
| Logroscino et al, 1997 [6]    | 19 years | 21% (38/184) | <1 year age, acute illness |
| Barnard et al, 1999 [22]      | Discharge 53 months | 9.6% (5/52) 15.4% (8/52) | Brain tumors, metabolic disorder, multi-organ failure |
| Mah et al, 1999 [10]          | 5 years | 2% SE group 1.5% in NSE group | Drug overdose, sepsis, disseminated tuberculosis, congenital heart disease |
| Waterhouse et al, 1999 [34]   | -     | 17.8% (5.2 in pediatric and 24%) | CNS infection, hypoxia, drug withdrawal, continuous SE |
| Berg et al, 2001 [9]          | 4 years | 1.6% (10/613) | Neurodegenerative conditions, coexisting medical conditions |
| Callenbach et al, 2001 [24]   | 4 years | 1.9% (9/472) | Respiratory insufficiency, RSV infection, aspiration, brain herniation |
| Kim et al, 2001 [43]          | 4 years | 43.5% (10/23) | Acute symptomatic etiology, especially anoxia |
| Sahin et al, 2001 [4]         | 8 years | 31.8% (7/22) | Remote symptomatic and progressive encephalopathy |
| Tabarki et al, 2001 [44]      | 7 years | 15.8% (22/139) | Acute symptomatic seizure, progressive encephalopathy |
| Logroscino G et al 2002 [39]  | Unclear | 43% | Prolonged SE (>24 hr), acute symptomatic etiology, myoclonic SE |
| Ogutu et al, 2002 [45]        | Discharge | 13.1% (5/38) | Intracranial hypertension, intractable convulsions |
| Sillanpää et al, 2002 [2]     | Long follow up | 16% (24/150) | Remote symptomatic cause, young patient (<6 yrs), partial seizures, history of febrile seizure |
| Singhi et al, 2002 [46]       | Discharge | 25% (10/40) | Early intubation and ventilation, meningoencephalitis, acute hyponatremia, hepatic encephalopathy |
| Wu et al, 2002 [3]            | Discharge | 1.9% (55/2885) | Female sex, older age (>75) |
| Karasalihoglu et al, 2003 [47]| 1 month | 7.2% (6/83) | Polypharmacy, discontinuation of AEDs, neuromotor retardation, generalized background abnormality on EEG |
| Berg et al, 2004 [30]         | Unclear | 2.1% (13/613) | Neurodegenerative disorder ± epileptic encephalopathy, prolonged SE |
| Chin et al, 2004 [26]         | Discharge | 5.1% (5/98) | Younger age, intubation, CNS infection, hyponatremia, hypoxia, sepsis, subdural hematoma |
| Asadi-Pooya et al, 2005 [48]  | Discharge | 10.4% (14/135) | Prolonged febrile seizure, CNS infection, metabolic/AED withdrawal, symptomatic epilepsy, prolonged stay |
| Brevoord et al, 2005 [25]     | Discharge | 5.7% (7/205) | Near drowning episode, pneumococcal meningitis, cardiac failure, brainstem tumor, hemorrhagic shock, metabolic defect |
| Gulati et al, 2005 [8]        | Discharge | 30% (9/30) | Prolonged SE (>45 min), septic shock |
important risk factor for death [13]. Similar findings have been noted in prospective [29] and retrospective [26] pediatric studies. Human immunodeficiency virus-associated encephalitis was identified as a cause of SE in one previous pediatric study [4]. In our present data sample, we found intracranial infections, such as viral encephalitis and infectious encephalopathy, to be associated with mortality. These factors did not emerge as independent risk factors for death in multivariate analysis in this series.

Other comorbidities. Brain herniation was associated with an increased risk of death. Transtentorial herniation was identified as a long-term cause of death in a prior retrospective pediatric study [24]. Similarly, subdural hematoma, noted as a cause of death in a previous pediatric case series [33], was associated with mortality in our study. However, these factors were not found to be a significant risk factor for death in multivariate analysis. Unlike prior studies [34], patients with status following drug withdrawal did not have a higher mortality rate in this dataset.

Procedures

Blood Transfusion. We identified blood transfusion as a factor for fatalities. This additional risk is probably not a result of the transfusion in itself but is likely a marker for the poor clinical condition of certain patients who subsequently require greater intervention. While this finding was not corroborated by prior research, studies investigating patients with related markers of disease severity, such as those investigating ICU patients, have similarly high death rates [8,25].

Mechanical Ventilation. The need for ventilatory support in convulsive SE may arise from poor respiratory drive resulting from seizure complications or in the context of pharmacological coma induction. The risk of death in mechanical ventilation may be related to the risk of aspiration and impaired mucociliary clearance, leading to pneumonia [35]. Additionally, mechanical ventilation is also associated with complications such as pneumothorax and ventilator-associated lung injury. We confirmed mechanical ventilation as an independent risk factor for death in SE. Mechanical ventilation was associated with death in a prospective study that included adolescents and children [36]. Similar findings were noted in a randomized control trial comparing antiepileptic medications in the treatment of SE [37].

Risk factors assessment in SE. We investigated diagnostic entities due to their known association with high risk of mortality. The KID mentions all diagnoses encountered during a hospital admission irrespective of the cause-effect relationship between SE and associated diagnoses. Entities such as near drowning, hemorrhagic shock, structural brain lesion, and hypoglycemia (likely causes of SE), as well as sepsis, prolonged mechanical ventilation, and transfusion (likely resulting from SE or its

Table 5. Cont.

| Author, Year and Study Design | Follow up | Mortality rate | Predictors/Risk Factors |
|-------------------------------|-----------|---------------|-------------------------|
| Kang et al, 2005 [23]         | Discharge | 3%            | Higher mortality in acute symptomatic SE versus remote symptomatic SE |
| Maegaki et al, 2005 [49]      | Discharge | 3.8% (9/241)  | Prolonged SE (>2 hr), moderate-severe asthma |
| Ozdemir et al, 2005 [11]      | Discharge | 19% (5/27)    | Acute symptomatic SE, progressive encephalopathy, underlying disease |
| Ahmad et al, 2006 [50]        | Discharge | 17.5% (N = 160) | Progressive infection, cerebral malaria, febrile convulsions, acute bacterial meningitis, metabolic derangements |
| Chen et al, 2006 [51]         | Discharge | 3.1% (7/226)  | Febrile illness, acute bacterial meningitis, progressive neurological disorders, intermittent SE |
| Morrison et al, 2006 [33]     | Discharge | 18% (3/17)    | Subdural hematoma, birth asphyxia, post-cardiac arrest |
| Hayashi et al, 2007 [52]      | Discharge | 2.1% (10/479) | Encephalitis, cerebrovascular disease |
| Muchochi et al, 2007 [53]     | Discharge | 11.54% (3/26) | Pre-existing cerebral malaria, convulsions |
| Mpimbaza et al, 2008 [54]     | Discharge | 6% (20/330)   | Malaria, severe malnutrition, immunosuppression, pneumonia |
| Sadarangani et al, 2008 [29]  | Discharge | Confirmed convulsive SE: 19% (11/58) Probable convulsive SE: 11% (13/120) | Acute bacterial meningitis, age <1 year, hypoglycemia, focal onset seizures |
| Siddiqui et al, 2008 [55]     | Discharge | 12% (15/125)  | Acute intracranial infections, age <5 years, prolonged SE (5.93±5.76 hours) |
| Lin et al, 2009 [56]          | Stay in ICU | 8.51% (12/141) | Febrile illness |
| Mei Li et al, 2009 [36]       | 1 month | 15.8% (32/203) | Mechanical ventilation, complications, SE duration after admission, hyponatremia, recurrent SE |
| Molinero et al, 2009 [27]     | Discharge | 13% (6/47)    | Infectious cause, cerebrovascular accident, long seizure duration |

AED – antiepileptic drug; SE – status epilepticus; CNS – central nervous system; ICU – intensive care unit; RSV – respiratory syncytial virus.
doi:10.1371/journal.pone.0047474.t005
treatment) increased mortality in children with convulsive SE. Awareness of these risks may thus promote more improved targeted management towards correcting these conditions.

**Challenges.** The findings of this study need to be interpreted in the setting of data acquisition and subsequent analysis. Misclassification of seizures and comorbidities in the ICD-9 coding system is a potential source of error, as it is with all large databases studies. Multiple criteria exist to diagnose SE. While the Working Group of SE of the Epilepsy Foundation of America defines SE as a seizure of at least 30 minutes duration or multiple seizures without full recovery of consciousness in between [1], other investigators advocate a cutoff time as short as five minutes [30]. Individual physicians may not use the same operational definitions, leading to variations in case reporting. The KID dataset lacks information on the timing of procedures, such as blood transfusion and intubation, which may also be important variables in determining the risk of death in SE. Patients who suffer from SE are noted to have an increased risk of dying that extends to weeks, and possibly years, after discharge [39]. This information is unavailable in the KID dataset. Because there are no unique patient identifiers in the KID dataset, it was not possible to account for multiple episodes of SE in the same patient. While neonates were included in this study, there is a lack of consensus on the definition of SE in these patients. This study was unable to investigate certain variables, such as seizure duration, and some etiologies, such as cerebrovascular accidents and malaria, which have been identified as important risk factors in other studies due to few numbers of these cases.

**Conclusion**

Convulsive SE is a rare but serious condition and results in approximately 0.1% of all pediatric inpatient hospital admissions. It is fatal in approximately 1% of cases. The rarity of this condition makes it a difficult subject to study. The use of large nationwide databases, such as the KID dataset permits identification of factors associated with increased mortality.

**References**

1. Working Group on Status Epilepticus (1993) Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America’s Working Group on Status Epilepticus. JAMA 270: 854–859.
2. Sillanpaa M, Shinnar S (2002) Status epilepticus in a population-based cohort with childhood-onset epilepsy in Finland. Ann Neurol 52: 303–310.
3. Wu YW, Shek DW, Garcia PA, Zhao S, Johnson SE (2002) Incidence and mortality of generalized convulsive status epilepticus in California. Neurology 58: 1070–1076.
4. Sahin M, Menache CG, Holmes GL, Riviello JJ (2001) Outcome of severe refractory status epilepticus in children. Epilepsia 42: 1461–1467.
5. Koubrous M, Aldhakabe A (2007) In-hospital mortality of generalized convulsive status epilepticus: a large US sample. Neurology 69: 886–893.
6. Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA (1997) Short-term mortality after a first episode of status epilepticus. Epilepsia 38: 1344–1349.
7. Agency for Healthcare Research and Quality (2011) Overview of the Kids’ Inpatient Database (KID): Available at: http://www.hcup-us.ahrq.gov/ kidoverview.jsp. Accessed 2011 Dec 20.
8. Gulati S, Kafur V, Sridhar MR (2005) Status epilepticus in Indian children in a tertiary care center. Indian J Pediatr 72: 105–108.
9. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, et al. (2001) Early development of intractable epilepsy in children: a prospective study. Neurology 56: 1445–1452.
10. Mah JK, Mah MW (1999) Pediatric status epilepticus: a perspective from Saudi Arabia. Pediatr Neurol 20: 364–369.
11. Ozdemir D, Gulez P, Uran N, Yendur G, Kavakli T, et al. (2005) Efficacy of continuous midazolam infusion and mortality in childhood refractory generalized convulsive status epilepticus. Seizure 14: 129–132.
12. Aicardi J, Chevrie J (1970) Convulsive status epilepticus in infants and children. A study of 239 cases. Epilepsia 11: 187–197.

The findings from this study suggest new directions for research. Research should be done to determine which interventions may lead to improved outcomes. More data are needed to ascertain risk factors for long-term mortality in pediatric SE. Parallel research using large groups of adults should be done to establish risk factors for poor outcomes in this group. This may also help to identify risk factors that overlap between pediatric and adult populations. Prospective multicenter studies evaluating children presenting in SE may assist in better determination of risk factors for death and identify those interventions which best promote patient survival.

Our results may also carry implications for improvement of patient care. It is likely that in-hospital mortality of SE is largely a function of the underlying cause of the SE, while other factors may also have an impact on outcome. Some of these risk factors may be ameliorated with specific therapy. Mild induced hypothermia, for example, may be beneficial in patients with near-drowning episodes [40]. Early identification and treatment of some of these aggravating factors may not only prevent immediate mortality, but it may also reduce long-term complications and limit neurological dysfunction. Beyond these implications, the development of treatment paradigms may also help reduce variability in care and outcomes and thereby decrease hospital costs. This research may lead the development of warning algorithms which may in turn promote early interventions that reduce ICU admissions, other medical complications, and even death. Identification of risk factors is thus an important first step towards providing improved care when caring for pediatric patients with SE.

**Acknowledgments**

The authors would like to acknowledge the Healthcare Cost and Utilization and Project (HCUP) for provision of the KID Inpatient Database for this study.

**Author Contributions**

Conceived and designed the experiments: TL TS SR DG ST AA MK. Performed the experiments: TS DG ST AA. Analyzed the data: TS DG ST AA. Wrote the paper: SR TL MK TS.

**Risk Factors for Death in Status Epilepticus**

1. Dunn DW (1988) Status epilepticus in children: etiology, clinical features, and outcome. J Child Neurol 3: 167–173.
2. DeLorenzo RJ, Towne AR, Pellock JM, Ko D (1992) Status epilepticus in children, adults, and the elderly. Epilepsia 33 Suppl 4: S15–25.
3. Banerjee PN, Hauser WA (2007) Incidence and Prevalence. In: Engel J, Pedley TA, Aicardi J, Dichter MA, Moshe S et al., editors. Epilepsy: A Comprehensive Textbook. Lippincott Williams & Wilkins. pp. 45–56.
4. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JF, Pellock JM, et al. (1996) A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 46: 1029–1035.
5. Knuie S, Rosenow F, Vescori M, Oestel WH, Mueller HH, et al. (2001) Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 42: 714–718.
6. Logroscino G, Hesdorffer DC, Cascino G, Hauser WA, Coeysa A, et al. (2005) Mortality after a first episode of status epilepticus in the United States and Europe. Epilepsia 46 Suppl 11: 46–48.
7. Aicardi J, Chevrie J (1970) Convulsive disorders in the first year of life: persistence of epileptic seizures. Epilepsia 20: 643–649.
8. Sharip A, Sorvillo F, Redelings MD, Mascola L, Wise M, et al. (2006) Population-based analysis of meningococcal disease mortality in the United States: 1990–2002. Pediatr Infect Dis 25: 191–194.
9. Day JF, Shamm J (2009) Severe winter freezes enhance St. Louis encephalitis virus amplification and epidemic transmission in peninsular Florida. J Med Virol 81: 787–794.
10. Barnard C, Wirtell E (1999) Does status epilepticus in children cause developmental deterioration and exacerbation of epilepsy? J Child Neurol 14: 787–794.
11. Kang DC, Lee YM, Lee J, Kim HD, Coo C (2005) Prognostic factors of status epilepticus in children. Yonsei Med J 46: 27–33.
24. Callenbach FM, Westendorp RG, Geerts AT, Arts WF, Peeters EA, et al. (2001) Mortality in children with epilepsy: the Dutch study of epilepsy in childhood. Pediatrics 107: 1259-1263.
25. Brevedo JD, Joosten KF, Arts WF, van Kooij RW, de Hoog M (2003) Status epilepticus: clinical analysis of a treatment protocol based on midazolam and phenytoin. J Child Neurol 20: 476-481.
26. Chin RF, Verhulst L, Neville BG, Peters MJ, Scott RC (2004) Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. J Neurol Neurosurg Psychiatry 75: 1584-1588.
27. Molinero MR, Holden KR, Rodriguez LC, Collins JS, Samra JA, et al. (2009) Pediatric convulsive status epilepticus in Honduras, Central America. Epilepsia 50: 2314-2319.
28. Kramer U, Shorer Z, Ben-Zeev B, Lerman-Sagie T, Goldberg-Stern H, et al. (2005) Severe refractory status epilepticus owing to presumed encephalitis. J Child Neurol 20: 104-117.
29. Sudarangan M, Seaton C, Scott JA, Ogutu B, Edwards T, et al. (2008) Incidence and outcome of convulsive status epilepticus in Kenyan children: a cohort study. Lancet Neurol 7: 145-150.
30. Berg AT, Shinnar S, Testa FM, Levy SR, Frobish D, et al. (2004) Status epilepticus after the initial diagnosis of epilepsy in children. Neurology 63: 1027-1034.
31. Ryan CA, Dowling G (1993) Drowning deaths in people with epilepsy. CMAJ 148: 781-784.
32. Wilson FC, Harpur J, Watson T, Morrow JJ (2003) Adult survivors of severe cerebral hypoxia: case series survey and comparative analysis. NeuroRehabilitation 18: 291-298.
33. Morrison G, Gibbou E, Whitehouse WP (2006) High-dose midazolam therapy for refractory status epilepticus in children. Intensive Care Med 32: 2070-2076.
34. Waterhouse EJ, Garnett LK, Towne AR, Morton LD, Barnes T, et al. (1999) Prospective population-based study of intermittent and continuous convulsive status epilepticus in Richmond, Virginia. Epilepsia 40: 752-758.
35. Konrad F, Schreiber T, Brecht-Kraus D, Georgieff M (1994) Mucociliary transport in ICU patients. Chest 105: 237-241.
36. Li JM, Chen L, Zhou B, Zhu Y, Wang JH, et al. (2009) Clinical features of status epilepticus in adults and adolescents of southwest China: mortality, etiology, and predictors of death. Epilepsy Behav 14: 146-149.
37. Prasad K, Krishnan PR, Al-Roomi K, Sequeira R (2007) Anticonvulsant Pharmacokinetics and clinical efficacy of lorazepam in children with severe malaria and convulsions. Br J Clin Pharmacol 65: 12-21.
38. Ahmad S, Ellis JC, Kamwendo H, Molynieux E (2006) Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial. Lancet 367: 1591-1597.
39. Chen L, Zhou B, Li JM, Zhu Y, Wang JH, et al. (2009) Clinical features of convulsive status epilepticus: a study of 228 cases in western China. Eur J Neurol 16: 444-449.
40. Hayashi K, Osawa M, Aihara M, Izumi T, Ohtsuka Y, et al. (2007) Efficacy of intravenous midazolam for status epilepticus in children. Pediatr Int 49: 366-372.
41. Maegaki Y, Kurozawa Y, Hanaki K, Ohno K (2005) Risk factors for fatality and neurological sequelae after status epilepticus in children. Neuropediatrics 36: 186-192.
42. Munchi SN, Obiero K, Newton CR, Ogutu BR, Edwards G, et al. (2008) Pharmacokinetics and clinical efficacy of lorazepam in children with severe malaria and convulsions. Br J Clin Pharmacol 65: 12-21.
43. Pujimba A, Ndezi G, Starek M, Byarugaba J (2008) Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. Pediatrics 121: 580-584.
44. Siddiqui TS, Anir u R, Jan MA, Waezer MS, Burki MK (2008) Status epilepticus: aetiology and outcome in children. J Ayub Med Coll Abbottabad 20: 10-15.
45. Lin KL, Lin JJ, Hsia SH, Wu CT, Wang HS (2009) Analysis of convulsive status epilepticus in children of Taiwan. Pediatr Neurol 41: 413-418.