Comparison of long-term survival with continued medical therapy, vagus nerve stimulation, and cranial epilepsy surgery in paediatric patients with drug-resistant epilepsy in the USA: an observational cohort study

Lu Zhang, Matt Hall, Sandi K Lam

Summary

Background Long-term survival in paediatric epilepsy is incompletely characterised. A better understanding of treatment effects on mortality in paediatric patients with drug-resistant epilepsy is needed for health-care decision making. We aimed to compare the long-term survival rates associated with antiseizure medications only, antiseizure medications plus vagus nerve stimulation (VNS), and antiseizure medications plus cranial epilepsy surgery in paediatric patients with drug-resistant epilepsy using a large national administrative database in the USA.

Methods In this observational cohort study, patients aged 0–17 years who were diagnosed with drug-resistant epilepsy using International Classificiaton of Diseases codes between Jan 1, 2004, and Dec 31, 2020, were identified from the Pediatric Health Information System, an administrative database that contains inpatient, emergency department, ambulatory, and observation unit encounter-level data from more than 49 children's hospitals in the USA. Patients treated with at least three types of antiseizure medications were included in the medical therapy cohort, those treated with antiseizure medications plus VNS were included in the VNS cohort, and those treated with antiseizure medications plus cranial epilepsy surgery were included in the surgery cohort. Participants were followed up until the date of their last clinical encounter, in-hospital death, or Dec 31, 2020. Inverse probability of treatment weighting (IPTW) was used to balance baseline demographics and clinical characteristics between treatment groups. The unconditional probabilities of survival were estimated by weighted Kaplan-Meier analysis. A weighted Cox proportional hazards model was used to investigate the association between risk of overall death and age, sex, geographical region, race and ethnicity, comorbidity, primary diagnosis, insurance, and treatment.

Findings This study included 10 240 patients treated with antiseizure medications only, 5019 patients treated with antiseizure medications plus VNS, and 3033 patients treated with antiseizure medications plus cranial epilepsy surgery. The median age of paediatric patients was 7 years (IQR 4–12) in the medical therapy cohort, 9 years (6–13) in the VNS cohort, and 9 years (5–13) in the surgery cohort. The IPTW-adjusted probabilities of surviving beyond 10 years were 89·27% (95% CI 87·71–90·85) for the medical therapy cohort, 92·65% (90·62–94·72) for the VNS cohort, and 98·45% (97·53–99·38) for the surgery cohort. The difference in survival probabilities was significant (log-rank p<0·0001). Compared with the medical therapy cohort, the IPTW-adjusted hazard ratio for overall death was 0·60 (95% CI 0·50–0·74) for the VNS cohort and 0·19 (0·10–0·33) for the surgery cohort.

Interpretation Paediatric patients with drug-resistant epilepsy who underwent cranial epilepsy surgery or VNS had a higher survival rate than those who received only medical treatment. These findings highlight the importance of a multidisciplinary comprehensive team approach to the treatment of epilepsy, which includes tailored evaluation and deployment of medical and surgical treatment options for patients with this challenging disease.

Funding None.

Lancet Child Adolesc Health 2023

Published Online
June 2, 2023
https://doi.org/10.1016/S2352-4642(23)00082-2

See Online/Comment
https://doi.org/10.1016/S2352-4642(23)00129-3

Department of Neurological Surgery, McGaw Medial Center of Northwestern University, Chicago, IL, USA (L Zhang PhD, Prof S K Lam MD); **Division of Pediatric Neurosurgery, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA** (L Zhang, Prof S K Lam); **Data and Biostatistics, Children's Hospital Association, Lenexa, KS, USA** (M Hall PhD)

Correspondence to:
Prof Sandi K Lam, Department of Neurological Surgery, Anne & Robert H Lurie Children's Hospital of Chicago, Chicago, IL 60611, USA
slam@luriechildrens.org

Introduction

Epilepsy is one of the most common neurological conditions, affecting at least 3·4 million people in the USA.[1,2] It is more common in children than in adults,[3] with a prevalence of 10·2 per 1000 children aged 0–18 years.[4] Among children with epilepsy, an estimated 20% have drug-resistant epilepsy,[4,5] defined as continued seizures in the setting of failure of two antiseizure medications to achieve sustained seizure freedom, providing that the two medications were appropriately chosen, adequately tolerated, and used as directed.[6] People with epilepsy have increased mortality rates compared with the age-matched population, with important direct causes of death being sudden unexplained death in epilepsy, suicide, accidents (eg, drowning and fire), and status epilepticus. Mortality in children and young adults with epilepsy is even higher than in adults with epilepsy.[7–10]

Research in context

Evidence before this study

We searched PubMed and Ovid MEDLINE for studies published up to Sept 30, 2021, which reported on the survival of paediatric patients with drug-resistant epilepsy. Search terms included "child", "children", "adolescent", "adolescence", "teen", "youth", "infant", "pediatric", "refractory epilepsy", "refractory seizure", "drug resistant epilepsy", "intractable epilepsy", "survival", and "mortality". Most previous studies compared the efficacy of treatments on seizure frequency, seizure duration, and quality of life. People with epilepsy have higher mortality rates than the general population. Studies evaluating the effects of treatments on survival rate in people with epilepsy are rare, and data are generally collected from a mixed population of children and adults. No studies have directly compared survival rates among paediatric patients with drug-resistant epilepsy receiving continued antiseizure medications, vagus nerve stimulation (VNS), and cranial epilepsy surgery.

Added value of this study

To our knowledge, this is the first large observational cohort study directly comparing long-term survival rates in paediatric patients with drug-resistant epilepsy treated with antiseizure medications only, antiseizure medications plus VNS, and antiseizure medications plus cranial epilepsy surgery. Survival was highest in patients who underwent cranial epilepsy surgery and lowest in those treated with antiseizure medications alone. Younger age, the presence of comorbidities, less focal epilepsy types, and non-surgical treatments were associated with higher hazard ratios for mortality. We also found disparities in access to paediatric epilepsy surgery; compared with patients receiving cranial epilepsy surgery and VNS, patients receiving antiseizure medications only were less likely to be identified as non-Hispanic White and less likely to be privately insured.

Implications of all the available evidence

By focusing on longitudinal survival in the paediatric population with drug-resistant epilepsy exposed to three common treatment modalities, our findings can help to inform health-care decision making. The evidence points to the importance of evaluating all treatment options provided at multidisciplinary comprehensive epilepsy centres and the need to consider candidacy for cranial epilepsy surgery or neurostimulation such as VNS. Disparities in access to epilepsy surgery needs to be explored further to identify multifactorial reasons and to improve health-care delivery and health equity in the treatment of paediatric epilepsy.

Cranial epilepsy surgery is an effective treatment option for paediatric patients with drug-resistant epilepsy. For example, in a single-centre, randomised, controlled trial in patients aged 0–18 years with drug-resistant epilepsy of various causes, 44 (77%) of 57 patients in the surgical group were seizure free, compared with four (7%) of 59 patients in the medical therapy group at 12 months.[11] Cranial epilepsy surgery has been shown internationally to be safe and effective, even for infants younger than 3 months.[12]

The causes of drug-resistant epilepsy are heterogeneous. Some patients might not be considered ideal candidates for resective cranial epilepsy surgery.[13] Those patients either continue medication therapy or can be candidates to receive stimulation approaches, including vagus nerve stimulation (VNS), responsive neurostimulation, and deep brain stimulation. Evidence-based clinical guidelines from the American Academy of Neurology in 2013 stated that VNS is an effective option for treating seizures.[14] A multicentre study found that VNS as an adjunct to best medical practice is superior to best medical practice alone in improving health-related quality of life for patients aged 16–75 years with drug-resistant epilepsy.[15]

The efficacy of antiseizure medications, VNS, and cranial epilepsy surgery in reducing seizure frequency, reducing seizure duration, and improving quality of life is well established. However, studies of long-term survival improvement are relatively rare and based on data collected from a mixed population of children and adults.[16–21] A better understanding treatment effects on mortality risk is needed for health-care decision making. In addition, the safety and efficacy profiles of medical treatments for children might be substantially different from adults due to differences in physiology and disease pathophysiology. Therefore, we aimed to compare the long-term survival rate associated with antiseizure medications only, antiseizure medications plus VNS, and antiseizure medications plus cranial epilepsy surgery in paediatric patients using a large national administrative database in the USA.

Methods

Study design and data sources

In this observational cohort study, data were obtained from the Children's Hospital Association's (Lenexa, KS, USA) Pediatric Health Information System (PHIS), an administrative database that contains inpatient, emergency department, ambulatory, and observation unit encounter-level data from more than 49 children's hospitals in the USA. The PHIS assigns each patient a unique identifier for subsequent encounters to allow longitudinal study. This study received exempt status as non-human subjects research with the Institutional Review Board at the Ann & Robert H Lurie Children's Hospital of Chicago (Chicago, IL, USA).

The study cohort was assembled in a five-step process. First, we retrospectively queried the PHIS database using International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) and tenth revision,

Clinical Modification (ICD-10-CM) codes. We extracted the data for paediatric patients aged 0–17 years who were discharged from hospital between Jan 1, 2004, and Dec 31, 2020, based on available data at the time of analysis, with diagnosis codes of epilepsy (ICD-9-CM code 345.XX and ICD-10-CM code G40.XXX) or seizure (ICD-9-CM code 780.3X and ICD-10-CM code R56.X or R56.XX). Second, patients were included if they met any previously published algorithms[22–26] reported for identifying epilepsy: ie, had at least two encounters with diagnosis code 345.XX or G40.XXX on separate dates in any visit (including inpatient, emergency department, or ambulatory care); had at least one encounter with diagnosis code 345.XX or G40.XXX and at least one separate encounter on a different date with diagnosis code 780.3X or R56.X or R56.XX; had a primary diagnosis code 345.XX or G40.XXX and a therapeutic category code indicating antiseizure medication; had at least two encounters with diagnosis code 780.3X, R56.X, or R56.XX and a code (or codes) for antiseizure medication; or had an inpatient or emergency department visit with a primary diagnosis code 345.XX or G40.XXX. Third, we selected patients with drug-resistant epilepsy from the above cohort using the diagnosis codes (appendix). Fourth, we checked the treatments of every patient by using current procedural terminology codes, procedure codes, PHIS supply codes, and generic drug codes. Patients who received cranial epilepsy surgery, VNS, or at least three types of antiseizure medications without any surgical treatment were selected at this step; these patients were then assigned to the medical therapy cohort if they received at least three types of antiseizure medications, to the VNS cohort if they received VNS plus any type of antiseizure medication, and to the surgery cohort if they received cranial epilepsy surgery plus any type of antiseizure medication. For the medical therapy cohort, the first encounter date of the third type of antiseizure medication was defined as the index date for the purpose of study tracking. The first admission date of VNS implantation was defined as the index date for the VNS cohort, and the first admission date of cranial epilepsy surgery was defined as the index date for the surgery cohort. To address the possibility of confounding of multiple surgical treatment modalities in this analysis, patients who had both VNS and cranial epilepsy surgery were excluded from this study. Finally, we excluded patients without a full year of data before the index date, patients whose index dates were before 2005 or after 2020, and patients with missing values on key variables. 1 year of data before the index date were used to obtain baseline information of included patients. Patients in this study were longitudinally followed up until the date of their last clinical encounter, in-hospital death, or Dec 31, 2020.

Outcomes

The outcome event was in-hospital death, as defined by a mortality disposition in PHIS. Overall survival was calculated from the time between the date of the index encounter and either the date of in-hospital death from any cause or last encounter in PHIS. Patients who were alive at the end of the study period or lost to follow-up were censored. Other variables extracted from PHIS included: treatment type (antiseizure medications only, antiseizure medications plus VNS, or antiseizure medications plus cranial epilepsy surgery); age at index date (<4 years, 4–11 years, or 12–17 years); sex (female or male); geographical region in the USA (midwest, northeast, south, or west); race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or others); presence of any paediatric complex chronic condition;[27] primary epilepsy diagnosis by coding (focal or partial epilepsy, generalised epilepsy, or others); and insurance (Medicaid, private, or others). In this study, ambulatory surgery and observation unit care were defined as outpatient care; complex chronic conditions were determined from the 1 year of data preceding the index encounter.

Statistical analysis

Frequencies and proportions were reported for all baseline characteristics. We used Pearson's χ^2 tests for bivariate comparisons of baseline characteristics across the three cohorts. Inverse probability of treatment

See Online for appendix

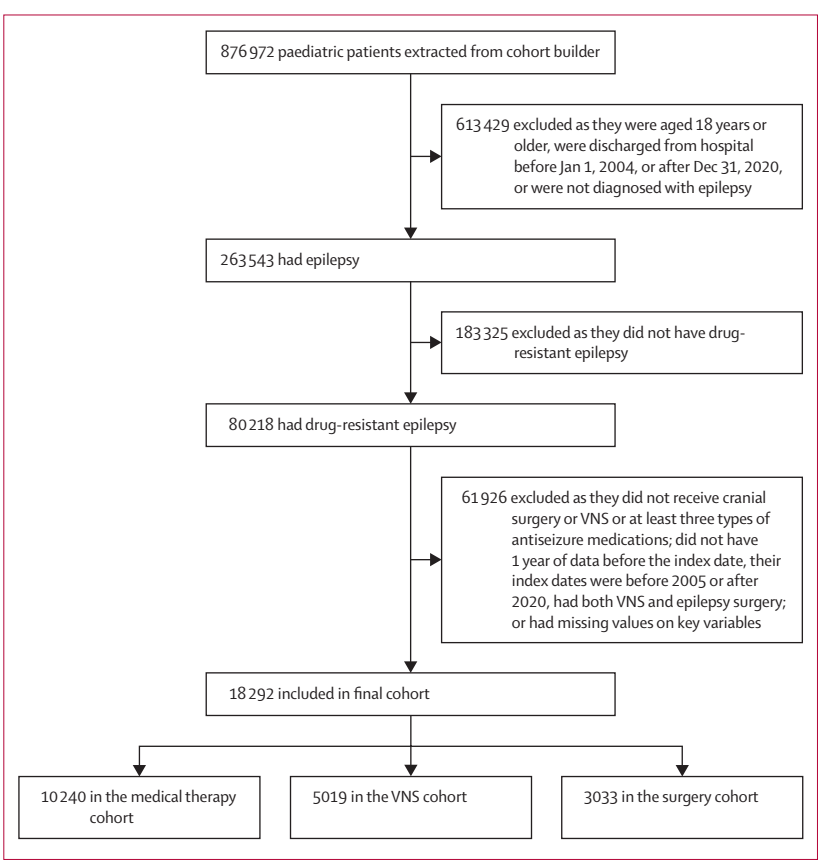

Figure 1: **Sample selection**
VNS=nagus nerve stimulation.

weighting (IPTW) using propensity score was used to balance baseline patient characteristics between the three cohorts by weighting each individual in the analysis.[28] We used multinomial logistic regression to calculate propensity scores by regressing treatment on age, sex, race and ethnicity, geographical region, insurance, comorbidity status, and primary diagnosis. We evaluated the covariate balance between three cohorts by comparing the absolute standardised mean differences in the baseline characteristics before and after weighting. Imbalance between treatment groups was defined as an absolute standardised mean difference greater than 0·1. We compared the difference in overall survival across treatment type cohorts using weighted Kaplan-Meier estimates with IPTW. Kaplan-Meier survival analysis estimates the unconditional probability of survival beyond time *t*, which can particularly address the issue of patients in the study having different lengths of follow-up.[29,30] We used the weighted log-rank test to examine significance of difference between groups. We used a Cox proportional hazards model with IPTW to investigate the association between risk of overall death and age, sex, geographical region, race and ethnicity, comorbidity, primary diagnosis, insurance, and treatment. The clustering effect of patients from different hospitals was taken into account by fitting a multilevel model.[31] We used the supremum test to test the proportional harzards assumption for all covariates,[32] and the results indicated that the proportional hazards assumption was valid for all variables. Results from the Cox model are summarised as hazard ratios (HRs). The significance level was set at p values of less than 0·05. Analyses were done with SAS (version 9.4) and R (version 4.2.2).

Role of the funding source

There was no funding source for this study.

	Total (n=18 292)	Medical therapy cohort (n=10 240)	VNS cohort (n=5019)	Surgery cohort (n=3033)	p value	Unweighted absolute standardised mean difference	Weighted absolute standardised mean difference
Age, years							
<4	3208 (17·5%)	2304 (22·5%)	463 (9·2%)	441 (14·5%)	<0·0001	0·29	0·02
4–11	9440 (51·6%)	5318 (51·9%)	2666 (53·1%)	1456 (48·0%)	..	..	..
12–17	5644 (30·9%)	2618 (25·6%)	1890 (37·7%)	1136 (37·5%)	..	..	..
Sex							
Male	9908 (54·2%)	5516 (53·9%)	2721 (54·2%)	1671 (55·1%)	0·49	0·02	0·01
Female	8384 (45·8%)	4724 (46·1%)	2298 (45·8%)	1362 (44·9%)	..	..	..
Geographical region							
Midwest	4743 (26·0%)	2607 (25·5%)	1335 (26·6%)	801 (26·4%)	0·0001	0·06	0·02
Northeast	2344 (12·8%)	1414 (13·8%)	561 (11·2%)	369 (12·3%)	..	..	..
South	6973 (38·1%)	3924 (38·3%)	1922 (38·3%)	1127 (37·2%)	..	..	..
West	4232 (23·1%)	2295 (22·4%)	1201 (23·9%)	736 (24·3%)	..	..	..
Race and ethnicity							
Non-Hispanic White	10 567 (57·8%)	5302 (51·8%)	3336 (66·5%)	1929 (63·6%)	<0·0001	0·21	0·01
Non-Hispanic Black	2678 (14·6%)	1887 (18·4%)	484 (9·6%)	307 (10·1%)	..	..	..
Hispanic	3640 (19·9%)	2240 (21·9%)	872 (17·4%)	528 (17·4%)	..	..	..
Other	1407 (7·7%)	811 (7·9%)	327 (6·5%)	269 (8·9%)	..	..	..
Comorbidity with complex chronic conditions							
No	4311 (23·6%)	3385 (33·1%)	624 (12·4%)	302 (10·0%)	<0·0001	0·39	0·03
Yes	13 981 (76·4%)	6855 (66·9%)	4395 (87·6%)	2731 (90·0%)	..	..	..
Primary diagnosis							
Focal or partial	2353 (12·9%)	895 (8·7%)	545 (10·9%)	913 (30·1%)	<0·0001	0·38	0·02
Generalised	1209 (6·6%)	664 (6·5%)	388 (7·7%)	157 (5·2%)	..	..	..
Other	14 730 (80·5%)	8681 (84·8%)	4086 (81·4%)	1963 (64·7%)	..	..	..
Insurance							
Medicaid	9372 (51·2%)	5719 (55·9%)	2431 (48·4%)	1222 (40·3%)	<0·0001	0·24	0·02
Private	7291 (39·9%)	3668 (35·8%)	2143 (42·7%)	1480 (48·8%)	..	..	..
Other	1629 (8·9%)	853 (8·3%)	445 (8·9%)	331 (10·9%)	..	..	..

Data are n (%) unless otherwise specified. The medical therapy cohort received only antiseizure medications, the VNS cohort received antiseizure medications plus VNS, and the surgery cohort received antiseizure medications plus cranial epilepsy surgery. VNS=vagus nerve stimulation.

Table 1: **Baseline patient demographics and clinical characteristics**

Results

We included 18 292 patients in the final cohort (figure 1): 10 240 patients in the medical therapy cohort, 5019 patients in the VNS cohort, and 3033 patients in the surgery cohort. Baseline patient demographics and clinical characteristics are shown in table 1. The proportion of males and females did not differ significantly in the three cohorts. Significant variations in age, geographical region, race and ethnicity, comorbidity with complex chronic conditions, primary diagnosis, and insurance were identified among the three cohorts. The median age of paediatric patients was 7 years (IQR 4–12) in the medical therapy cohort, 9 years (6–13) in the VNS cohort, and 9 years (5–13) in the surgery cohort. Compared with patients in the surgery cohort and VNS cohort, those in the medical therapy cohort were less likely to be living in the midwest and west regions, identified as non-Hispanic White, have focal or partial epilepsy as the primary coded diagnosis, and be privately insured (table 1). After the IPTW-adjusted analysis, the three groups were comparable, and all weighted absolute standardised mean differences were less than 0·1.

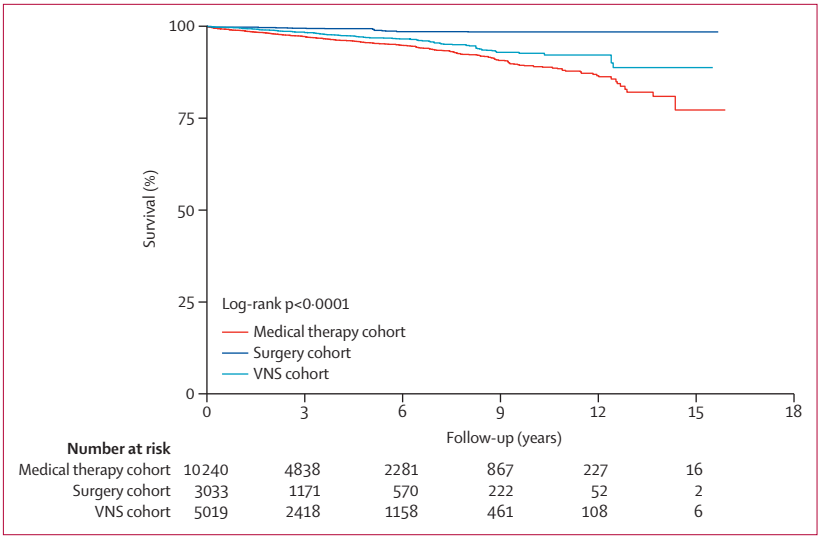

Figure 2: **Weighted Kaplan-Meier curves for paediatric patients with drug-resistant epilepsy**
The medical therapy cohort received only antiseizure medications, the VNS cohort received antiseizure medications plus VNS, and the surgery cohort received antiseizure medications plus cranial epilepsy surgery. VNS=vagus nerve stimulation.

By Dec 31, 2020, 367 (3·6%) of 10 240 patients in the medical therapy cohort, 113 (2·3%) of 5019 patients in the VNS cohort, and 17 (0·6%) of 3033 patients in the cranial epilepsy surgery cohort had died. The average follow-up time was 44·3 months (95% CI 43·5–45·1) for the medical therapy cohort, 44·3 months (43·2–45·5) for the VNS cohort, and 36·7 months (35·3–38·2) for the surgery cohort. The unconditional probability of surviving beyond 5 years was 95·51% (95% CI 94·91–96·11) for the medical therapy cohort, 96·83% (96·04–97·62) for the VNS cohort, and 99·35% (98·88–99·82) for the surgery cohort (figure 2). The unconditional probability of surviving beyond 10 years was 89·27% (95% CI 87·71–90·85) for the medical therapy cohort, 92·65% (90·62–94·72) for the VNS cohort, and 98·45% (97·53–99·38) for the surgery cohort (figure 2). The difference in the estimate of survival probabilities among the three cohorts was significant (p<0·0001).

In the univariable analysis, risk of overall death correlated with age, baseline comorbidities, primary coded diagnosis, and treatment type (table 2). Based on the multivariable cox model, compared with patients in the medical therapy cohort, the risks of overall death were reduced for patients in the VNS cohort (HR 0·60 [95% CI 0·50–0·74]) and for patients in the surgery cohort (0·19 [0·10–0·33]; table 2). Patients aged 4–11 years had a reduced risk of overall death compared with patients younger than 4 years old (HR 0·68 [95% CI 0·51–0·89; table 2). Patients with baseline comorbidities had a greater risk of death than patients without comorbidities (HR 4·31 [95% CI 1·78–10·44]; table 2). Likewise, patients with other types of epilepsy as the primary coded diagnosis had a greater risk of death than patients who had focal or partial epilepsy (HR 1·67 [95% CI 1·14–2·44]; table 2). Sex, geographical region, race and ethnicity, and insurance type were not significantly associated with differences in the risk of overall death (table 2).

Discussion

This is the first retrospective study comparing the long-term survival in paediatric patients with drug-resistant epilepsy among cohorts receiving antiseizure medications only, antiseizure medications plus VNS, and antiseizure medications plus cranial epilepsy surgery. We found significant difference in survival rate among the three cohorts. Paediatric patients with drug-resistant epilepsy who underwent cranial epilepsy surgery had the highest survival rate, and those in the medical therapy cohort had the lowest survival rate. These findings suggest a mortality benefit with surgical treatments in paediatric patients with drug-resistant epilepsy and point to the importance of multidisciplinary diagnostic and treatment approaches for these patients, such as those offered at comprehensive epilepsy centres where surgery is a part of the treatment options for epilepsy. However, a previous study in the USA found that fewer than 1% of patients of all ages with drug-resistant epilepsy were referred to comprehensive epilepsy centres.[33] The US Centers for Disease Control and Prevention and the National Academy of Medicine estimated that epilepsy surgery is underutilised to a catastrophic degree, with between 100 000 and 200 000 indicated surgeries for patients of all ages not occurring.[34] In light of our findings, we posit that this underutilisation of epilepsy surgery might directly lead to avoidable premature deaths in paediatric patients with epilepsy each year.

	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Age, years		
<4	1 (ref)	1 (ref)
4–11	0·64 (0·48–0·85)	0·68 (0·51–0·89)
12–17	0·85 (0·62–1·17)	0·90 (0·67–1·22)
Sex		
Male	1 (ref)	1 (ref)
Female	1·11 (0·86–1·42)	1·12 (0·89–1·42)
Geographical region		
Midwest	1 (ref)	1 (ref)
Northeast	1·19 (0·73–1·93)	1·23 (0·81–1·92)
South	0·97 (0·69–1·36)	0·99 (0·69–1·45)
West	1·07 (0·65–1·77)	1·15 (0·72–1·82)
Race and ethnicity		
Non-Hispanic White	1 (ref)	1 (ref)
Non-Hispanic Black	1·18 (0·81–1·71)	1·18 (0·80–1·73)
Hispanic	1·21 (0·89–1·65)	1·19 (0·84–1·68)
Other	1·32 (0·81–2·15)	1·30 (0·83–2·05)
Comorbidity with complex chronic conditions		
No	1 (ref)	1 (ref)
Yes	4·47 (1·91–10·45)	4·31 (1·78–10·44)
Primary diagnosis		
Focal or partial	1 (ref)	1 (ref)
Generalised	1·14 (0·71–1·82)	1·29 (0·82–2·03)
Other	1·75 (1·19–2·58)	1·67 (1·14–2·44)
Insurance		
Medicaid	1 (ref)	1 (ref)
Private	0·87 (0·72–1·05)	0·93 (0·78–1·11)
Other	0·93 (0·67–1·29)	0·96 (0·71–1·30)
Treatment		
Antiseizure medications only	1 (ref)	1 (ref)
Antiseizure medications plus cranial epilepsy surgery	0·18 (0·10–0·32)	0·19 (0·10–0·33)
Antiseizure medications plus VNS	0·64 (0·53–0·77)	0·60 (0·50–0·74)

VNS=vagus nerve stimulation. *Adjusted for age, sex, geographical region, race and ethnicity, comorbidity, primary diagnosis, insurance, and treatment.

Table 2: **Weighted Cox proportional hazards model for death in paediatric patients with drug-resistant epilepsy**

No studies so far have directly compared survival rates among paediatric patients with drug-resistant epilepsy receiving continued medical therapy, VNS, and cranial epilepsy surgery. Few studies have compared medical therapy with surgery. Vickrey and colleagues reported a mortality rate of 0·2 for medically treated patients over a period of 6 years, which was 0·13 times higher than surgically treated adult and paediatric patients at a single institution.[16] By contrast, Stavem and Guldvog found no significant difference in mortality of epilepsy patients of all ages with medical treatment and surgery,[18] providing insight into Norway's population over four decades starting in the late 1940s. Our study adds novel information with paediatric patients exposed to three treatment strategies for drug-resistant epilepsy.

Survival in patients with drug-resistant epilepsy treated with VNS has not been widely investigated. Champeaux and colleagues looked at a cohort of 101 patients with epilepsy of all ages who had been treated with VNS between 1999 and 2010: survival probability was 99% (95% CI 97–100) at 1 year, 96% (93–100) at 2 years, and 88% (80–97) at 5 years.[19] Annegers and colleagues analysed 1819 patients of all ages with VNS implantation and reported the crude mortality rate of 7·9 per 1000 per year and standard mortality rate of 3·6 (95% CI 2·3–5·4) with 2 years of follow-up.[35] The same group of investigators found a lower standard mortality rate with longer follow-up.[20] Mortality outcomes have also been estimated in 466 patients of all ages treated with VNS from 1995 to 2010: 29 deaths occurred, with an overall standard mortality rate of 6·4 (95% CI 4·5–9·2).[21]

We found multiple other variables associated with mortality hazard ratio. Patients aged 4–11 years had a lower risk of overall death compared with patients younger than 4 years. This finding warrants further study. It is possible that younger patients with drug-resistant epilepsy might have more severe forms of epilepsy (such as genetic epilepsies) and more comorbidities. This idea might also be consistent with the higher mortality in patients with chronic complex conditions. In addition, patients classified as having other types of epilepsy as the primary coded diagnosis had almost twice the mortality risk compared with those who were coded with focal or partial epilepsy. This finding is difficult to interpret: examples of codes falling into the "other" category (not focal or partial and not generalised) for analysis include G40.803 (other epilepsy, intractable, with status epilepticus) and G40.804 (other epilepsy, intractable, without status epilepticus), among others (G40.5x–G40.9x). Lennox Gastaut syndrome also falls within this "other" category, even though there can be features of focal and of generalised epilepsy in individual cases. This level of coding granularity for epilepsy is recognised to be dissatisfying from a clinical standpoint and is a known limitation of working with administrative data in epilepsy. These findings serve to motivate future clinical studies.

We found disparities in access to paediatric epilepsy surgery care. Compared with patients in the cranial epilepsy surgery and VNS cohorts, those in the medical therapy cohort were significantly less likely to be identified as non-Hispanic White and less likely to be privately insured. In single-institution retrospective studies, disparities by ethnoracial and socioeconomic factors, and by insurance status, have been found in access to paediatric epilepsy surgery.[36,37] Here, we show disparities in access to subspeciality neurosurgical care for paediatric patients with epilepsy on a national scale. Further studies to identify the causes of these disparities and inequities, and to explore subsequent implementation to reduce barriers to care are imperative. The

consequences of decreased access to epilepsy surgery options might affect survival.

The improved survival among the surgical cohorts need to be explored further in the context of counselling for patients and families about risks and benefits of surgery. Patients and families are receptive to candid information about mortality risks in epilepsy.[38] However, fewer than 10% of neurologists discuss these risks routinely with patients with epilepsy. Reasons cited include neurologists perceiving the risks to be rare and feeling that conversations scare patients unnecessarily, without offering preventive options. This situation persists despite American Academy of Neurology practice guidelines recommending that clinicians inform their paediatric epilepsy patients' parents or guardians of mortality risks in epilepsy.[39,40] The potential survival benefit associated with surgical interventions shown, as found in this study, accentuates the importance of awareness.

Improving early referral for comprehensive epilepsy evaluation is necessary to limit deleterious effects of ongoing seizures in the developing brain and to decrease time between surgery and seizure onset. We show that children's lives might depend on it. With innovation in paediatric epilepsy surgery, matching strides can be made in public health and health-care delivery. There is time-sensitive urgency to achieve seizure freedom in children when compared with adults: childhood seizures are associated with developmental arrest or regression, particularly in children younger than 2 years.[12,41] However, for patients with epilepsy of all ages, there are documented delays in referral for epilepsy surgery evaluation despite evidence from randomised controlled trials supporting the role of surgery in the management of drug-resistant epilepsy[35] and its effect on improved survival over time.[36] Providers, patients, families, and stakeholders need to know what is at stake.

There are limitations to this study. Errors in coding or documentation in the medical record are inherent with use of administrative data. This limitation is mitigated by the internal data verification process that upholds the quality of the PHIS data programme, such as for the reliability of the death variable, as well as the necessity of economic transactions. Billable services, products, and drugs are likely to be recorded. Granularity of clinical detail and rationale for clinical decision making cannot be gleaned from these data. Codes in existence for the years under study do not reliably define specifications for more recent surgical techniques, such as stereoelectroencephalography with depth electrodes, MRI-guided laser interstitial thermal therapy, endoscopy-assisted epilepsy surgery, or responsive neurostimulation implantation. Such techniques could not be studied separately in the time period examined. We evaluated data spanning more than 15 years, a period that has seen an evolution in clinical care, treatments, and health-care delivery by individual providers, institutions, and systems. PHIS hospital membership and data structure, as well as accreditation for comprehensive epilepsy centres, also grew during this time. More than 85% of children's hospitals contributing to PHIS data were also accredited as paediatric level 3 or level 4 with the US National Association of Epilepsy Centers, suggesting availability of multidisciplinary comprehensive paediatric epilepsy care. Implementation details are not known. This analysis of observational data can establish correlations but not causal relationships. Mortality is probably underestimated in this study because only deaths during a hospital encounter were included. The study population was drawn from the USA and might not be representative of other countries. The PHIS database contains data from more than 49 paediatric hospitals in the USA and is therefore broadly representative of the US paediatric population.

From a clinical care standpoint, administrative data cannot substitute for clinical research data. However, a nationwide view can be valuable in showing patterns for further examination in clinical practice settings. Findings from these larger samples can also inform future clinical trial design when appropriate. Although methods for defining cohorts with drug-resistant epilepsy have been established from administrative data, the study design of comparison cohorts is based on assumptions. Antiseizure medication dosages, side-effects, and compliance are not known. Dates of initial diagnosis for drug-resistant epilepsy for each patient in the studied hospital systems might not be exact in medical records because drug-resistant epilepsy is a chronic illness.

In conclusion, our findings suggest a mortality benefit with surgical treatments in paediatric patients with drug-resistant epilepsy. These findings highlight the importance of the multidisciplinary comprehensive team approach to the treatment of epilepsy, which includes tailored evaluation and deployment of medical and surgical treatment options for patients with this challenging disease. Epilepsy is a devastating diagnosis on patients and their families' health and quality of life. Continued research on all fronts—from basic science, translational, clinical trial, health services, and policy perspectives—are warranted.

Contributors

SKL and LZ designed the study. LZ conducted all statistical analyses and produced figures and tables. LZ and SKL co-wrote the initial draft. MH helped with data collection and interpretation. All authors had full access to and verified the data. All authors approved the final manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Patient data are not available to be shared publicly.

References

1 Hauser WA, Hesdorffer DC. Epilepsy: frequency, causes and consequences. New York, NY: Demos, 1990.

2 Engel J Jr. What can we do for people with drug-resistant epilepsy? The 2016 Wartenberg Lecture. *Neurology* 2016; **87:** 2483–89.

3 Cowan LD, Bodensteiner JB, Leviton A, Doherty L. Prevalence of the epilepsies in children and adolescents. *Epilepsia* 1989; **30:** 94–106.

4 Wirrell EC. Predicting pharmacoresistance in pediatric epilepsy. *Epilepsia* 2013; **54** (suppl 2)**:** 19–22.

5 Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. *Pediatrics* 2012; **129:** 256–64.

6 Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010; **51:** 1069–77.

7 Moseley BD, Wirrell EC, Wong-Kisiel LC, Nickels K. Early onset epilepsy is associated with increased mortality: a population-based study. *Epilepsy Res* 2013; **105:** 410–14.

8 Forsgren L, Hauser WA, Olafsson E, Sander JWAS, Sillanpää M, Tomson T. Mortality of epilepsy in developed countries: a review. *Epilepsia* 2005; **46** (suppl 11)**:** 18–27.

9 Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med* 2010; **363:** 2522–29.

10 Sillanpää M, Shinnar S. SUDEP and other causes of mortality in childhood-onset epilepsy. *Epilepsy Behav* 2013; **28:** 249–55.

11 Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for drug-resistant epilepsy in children. *N Engl J Med* 2017; **377:** 1639–47.

12 Roth J, Constantini S, Ekstein M, et al. Epilepsy surgery in infants up to 3 months of age: safety, feasibility, and outcomes: a multicenter, multinational study. *Epilepsia* 2021; **62:** 1897–906.

13 The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology* 1995; **45:** 224–30.

14 Morris GL 3rd, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2013; **81:** 1453–59.

15 Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. *Epilepsia* 2014; **55:** 893–900.

16 Vickrey BG. Mortality in a consecutive cohort of 248 adolescents and adults who underwent diagnostic evaluation for epilepsy surgery. *Epilepsia* 1997; **38** (suppl)**:** S67–69.

17 Pan I, LoPresti MA, Clarke DF, Lam S. The effectiveness of medical and surgical treatment for children with refractory epilepsy. *Neurosurgery* 2020; **88:** E73–82.

18 Stavem K, Guldvog B. Long-term survival after epilepsy surgery compared with matched epilepsy controls and the general population. *Epilepsy Res* 2005; **63:** 67–75.

19 Champeaux C, Marchal C, Valton L. [Vagus nerve stimulation for intractable epilepsy: a retrospective bicentric cohort study of 101 patients operated on between 1999 and 2010]. *Neurochirurgie* 2016; **62:** 146–50.

20 Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. *Epilepsia* 2000; **41:** 549–53.

21 Granbichler CA, Nashef L, Selway R, Polkey CE. Mortality and SUDEP in epilepsy patients treated with vagus nerve stimulation. *Epilepsia* 2015; **56:** 291–96.

22 Baaj AA, Benbadis SR, Tatum WO, Vale FL. Trends in the use of vagus nerve stimulation for epilepsy: analysis of a nationwide database. *Neurosurg Focus* 2008; **25:** E10.

23 Helmers SL, Thurman DJ, Durgin TL, Pai AK, Faught E. Descriptive epidemiology of epilepsy in the U.S. population: a different approach. *Epilepsia* 2015; **56:** 942–48.

24 Jetté N, Reid AY, Quan H, Hill MD, Wiebe S. How accurate is ICD coding for epilepsy? *Epilepsia* 2010; **51:** 62–69.

25 Kee VR, Gilchrist B, Granner MA, Sarrazin NR, Carnahan RM. A systematic review of validated methods for identifying seizures, convulsions, or epilepsy using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012; **21** (suppl 1)**:** 183–93.

26 Pestana Knight EM, Schiltz NK, Bakaki PM, Koroukian SM, Lhatoo SD, Kaiboriboon K. Increasing utilization of pediatric epilepsy surgery in the United States between 1997 and 2009. *Epilepsia* 2015; **56:** 375–81.

27 Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr* 2014; **14:** 199.

28 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015; **34:** 3661–79.

29 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.

30 de Tisi J, Bell GSMD, Peacock JLP, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet* 2011; **378:** 1388–95.

31 Rabe-Hesketh S, Skrondal A. Anders. Multilevel modelling of complex survey data. *J R Stat Soc Ser A Stat Soc* 2006; **169:** 805–27.

32 Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of Martingale-based residuals. *Biometrika* 1993; **80:** 557–72.

33 Engel J Jr. The current place of epilepsy surgery. *Curr Opin Neurol* 2018; **31:** 192–97.

34 National Association of Epilepsy Centers. Data on specialized epilepsy centers: report to the Institute of Medicine's Committee on the Public Health Dimensions of the Epilepsies. In: England MJ, Liverman CT, Schultz AM, Strawbridge LM, eds. Epilepsy across the spectrum. Washington, DC: National Academies Press, 2012: 509–16.

35 Annegers JF, Coan SP, Hauser WA, Leestma J, Duffell W, Tarver B. Epilepsy, vagal nerve stimulation by the NCP system, mortality, and sudden, unexpected, unexplained death. *Epilepsia* 1998; **39:** 206–12.

36 Hauptman JS, Dadour A, Oh T, et al. Sociodemographic changes over 25 years of pediatric epilepsy surgery at UCLA. *J Neurosurg Pediatr* 2013; **11:** 250–55.

37 Jackson HN, Gadgil N, Pan IW, et al. Sociodemographic factors in pediatric epilepsy surgery. *Pediatr Neurol* 2020; **107:** 71–76.

38 Gayatri NA, Morrall MCHJ, Jain V, Kashyape P, Pysden K, Ferrie C. Parental and physician beliefs regarding the provision and content of written sudden unexpected death in epilepsy (SUDEP) information. *Epilepsia* 2010; **51:** 777–82.

39 Friedman D, Donner EJ, Stephens D, Wright C, Devinsky O. Sudden unexpected death in epilepsy: knowledge and experience among U.S. and Canadian neurologists. *Epilepsy Behav* 2014; **35:** 13–18.

40 Harden C, Tomson T, Buchalter J, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors. *Neurology* 2017; **88:** 1674–80.

41 Asarnow RF, LoPresti C, Guthrie D, et al. Developmental outcomes in children receiving resection surgery for medically intractable infantile spasms. *Dev Med Child Neurol* 1997; **39:** 430–40.