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Reduced long-term mortality after successful resective epilepsy surgery: a population-based study

Cecilia Granthon ,[1,2] Anna Edelvik Tranberg,[1,2] Kristina Malmgren,[1,2] Maria Compagno Strandberg,[3] Eva Kumlien,[4] Petra Redfors[1,2]

[1]Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[2]Department of Neurology, Member of the ERN EpiCARE, Sahlgrenska University Hospital, Gothenburg, Sweden
[3]Division of Neurology, Department of Clinical Sciences, Lund University Hospital, Lund, Sweden
[4]Department of Medical Sciences, Neurology, Uppsala University, Uppsala, Sweden

Correspondence to
Dr Petra Redfors, Department of Clinical Neuroscience, University of Gothenburg Institute of Neuroscience and Physiology, Gothenburg, Sweden; petra.redfors@vgregion.se

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ABSTRACT

Background We investigated all-cause and epilepsy-related mortality in patients operated with resective epilepsy surgery and in non-operated patients with drug-resistant epilepsy. Our hypothesis was that patients who proceed to surgery have lower mortality over time compared with non-operated patients.

Method Data from 1329 adults and children from the Swedish National Epilepsy Surgery Register and 666 patients with drug-resistant epilepsy who had undergone presurgical work-up but not been operated were analysed. The operated patients had follow-ups between 2 and 20 years. We used the Swedish Cause of Death Register to identify deaths. Autopsy reports were collected for patients with suspected sudden unexpected death in epilepsy (SUDEP). Kaplan-Meier and Cox regression analyses were performed to identify predictors for mortality and SUDEP.

Results SUDEP accounted for 30% of all deaths. Surgery was associated with lower all-cause mortality (HR 0.7, 95% CI 0.5 to 0.9), also when adjusted for age, sex and tonic–clonic seizures at inclusion. The benefit of surgery seemed to persist and possibly even increase after 15 years of follow-up. Risk factors of mortality for operated patients were persisting seizures and living alone. Of the operated patients, 37% had seizures, and these had a higher risk of mortality (HR 2.1, 95% CI 1.4 to 3.0) and SUDEP (HR 3.5, 95% CI 1.7 to 7.3) compared with patients with seizure freedom at last follow-up.

Conclusions In this large population-based epilepsy surgery cohort, operated patients had a lower all-cause mortality compared with non-operated patients with drug-resistant epilepsy. Seizure freedom was the most important beneficial factor for both all-cause mortality and SUDEP among operated patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several smaller studies have indicated that operated patients have reduced mortality compared with non-operated patients with drug-resistant epilepsy.

WHAT THIS STUDY ADDS

⇒ To the best of our knowledge, this is the largest population-based study to date. Patients who had undergone resective epilepsy surgery had 30% reduced mortality compared with non-operated patients. Tonic–clonic seizures at follow-up were associated with almost five times higher risk of sudden unexpected death in epilepsy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Epilepsy surgery is still an underused treatment option. The reduced risk for mortality after resective epilepsy surgery further emphasises the importance of considering this treatment option for patients with drug-resistant epilepsy.

INTRODUCTION

About 70 000 people in Sweden have active epilepsy[1–3] and 30% (approximately 21 000) are refractory to antiseizure medication (ASM). After the second ASM, the chance for seizure freedom with one more ASM has been estimated to be at most 5%–10% per year.[4] Compared with the general population, mortality rates are higher in persons with epilepsy. This is especially true for those with frequent seizures and an underlying focal cause.[5 6] The annual estimated incidence of sudden unexpected death in epilepsy (SUDEP) in epilepsy patients is 1.16 per 1000 persons. This means that if a person has had epilepsy since infancy, the cumulative risk is as high as 8% by the age of 70 years.[7] Frequent tonic–clonic seizures (TCS) and having had TCS in the preceding years have been identified as risk factors of SUDEP.[8–11] Moreover, living alone was associated with SUDEP in a population-based study in Sweden.[10] Epilepsy surgery is a well-established treatment option for carefully selected patients with excellent short-term and long-term seizure outcome.[12–15] Epilepsy surgery reduces seizure frequency for individuals with persisting seizures and renders many patients seizure free. The available evidence suggests that operated patients may have a reduced mortality including SUDEP. However, existing studies of mortality and causes of death for operated versus non-operated drug-resistant patients are limited and several are based on surgical series from 1950s to 1990s.[16–23] Additionally, information on preoperative seizure frequency, seizure type and surgery type is often scarce. The aim of this study was to investigate mortality after epilepsy surgery in adults and children in a large population-based group of operated and non-operated patients with epilepsy. We further assessed the proportion of patients who died from epilepsy related causes, including SUDEP, in both cohorts. Our hypothesis was that patients who proceed to surgery have lower mortality

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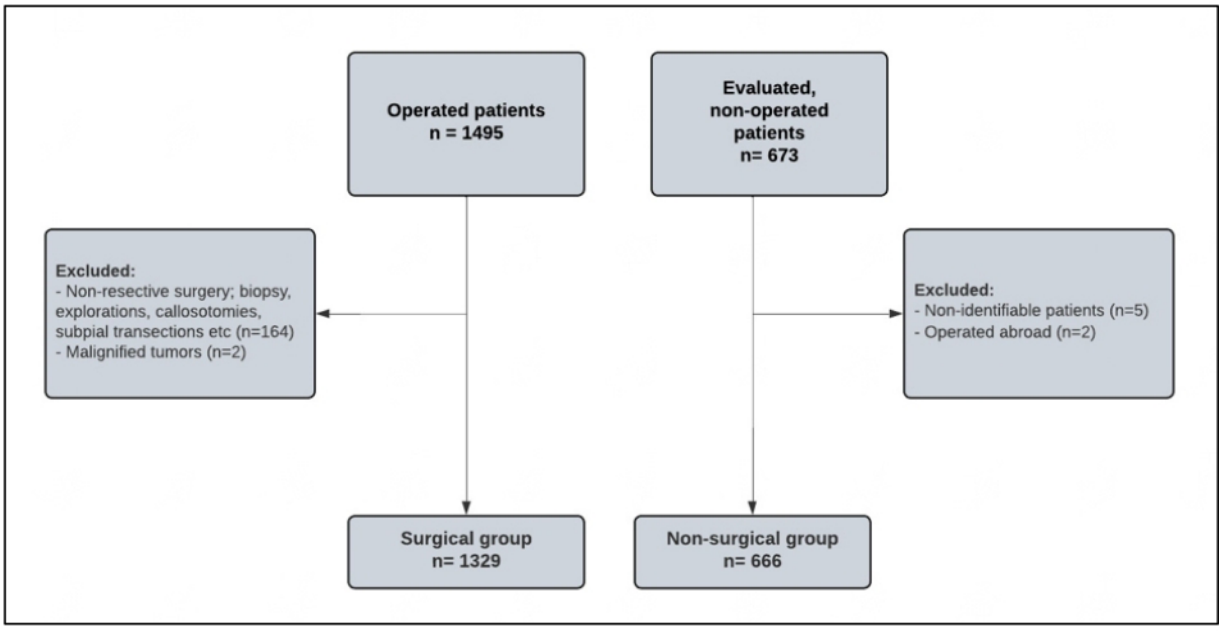

Figure 1 Flow chart of operated and non-operated patients.

compared with patients who have not been subject to surgical treatment.

METHODS

Study cohorts

The study population and reasons for exclusion are illustrated in figure 1.

Surgical group

This study is based on prospectively collected data from The Swedish National Epilepsy Surgery Register (SNESUR). This is a population-based register covering all epilepsy surgery procedures in Sweden from 1990 onwards.[14] We included patients who had undergone resective epilepsy surgery from 1 January 1990 to 30 November 2019. Inclusion date was set as the time of surgery. Follow-up visits were conducted 2 years after surgery. Long-term follow-up using structured telephone interviews every 5 years after surgery was initiated in 2005 for patients operated 1995 or later. Thus, patients operated 1995–1999 had their first long-term follow-up after 10 years and patients operated 2000 and later had follow-ups every 5 years. Patients operated 1990–1994 only had 2-year follow-up. Patients operated after 30 November 2017 were only included regarding baseline data and mortality outcome. In case of repeated surgery, follow-up data were collected after the last surgery.

Non-surgical group

We used non-operated patients as a comparison group. This group consisted of (1) patients entered into SNESUR, who were evaluated for epilepsy surgery but declined or were deemed unsuitable for operation (n=442) and (2) retrospectively identified adult (≥18 years) patients from three of the surgical centres (Lund, Uppsala and Gothenburg), who had undergone presurgical investigation between 1990 and 2016 but not been offered surgery and who had not been entered into SNESUR (n=224). All non-operated patients had drug-resistant epilepsy. Inclusion date was set at the date when the decision to refrain from surgery was made. Baseline data for all non-operated patients were collected from their presurgical evaluation. The non-operated patients had no follow-ups within the framework of our study.

Baseline and follow-up variables

The following baseline data were included for both cohorts: age at inclusion, sex, age at epilepsy onset, living conditions, level of education, number of tried ASMs (except for 220 non-operated patients for whom ASM data were incomplete), seizure frequency for all seizure types (auras excluded) and seizure frequency for TCS during the year preceding investigations. For patients>16 years, education level was defined as the highest achieved level and categorised into compulsory school (9 years), high school (3 years following the compulsory 9 years or vocational education), postsecondary education (university or college) and adapted schooling for students with intellectual disabilities. For the retrospectively identified non-operated patients, we also identified reasons for not being operated.[24] For the operated patients, we collected data on type of surgery, localisation and histopathology.

Outcome data were collected from the last available follow-up: seizure frequency for all seizure types (auras excluded) and seizure frequency for TCS during the year preceding follow-up, as well as living conditions. Seizure freedom was defined as being seizure free at least the year before follow-up, auras excluded.

Causes of death

The unique Swedish personal identity number was used to ascertain dates of death, main causes of death and contributing causes of death from the Swedish Cause of Death Register.[25] This register also includes information on the place of death (at home or in hospital) and whether an autopsy was performed or not. We collected autopsy reports for patients with a sudden, unexplained death and/or cardiac death and/or epilepsy mentioned on the medical certificate of cause of death (n=63). For operated adult patients who were not autopsied, we used the Swedish National Patient Register. It includes all inpatient stays at hospital and the diagnoses the patients had been hospitalised for.[26] For patients from Region Västra Götaland, medical

records were reviewed. All data on potential SUDEP patients were reviewed by the first and last author (CG and PR) and classified through consensus agreement. Seven autopsy reports where there were doubts about the cause of death were discussed with a pathologist. Additional information on the cause of death for 10 patients was kindly shared from the authors of 2 earlier Swedish studies.[9 20]

SUDEP definition

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death.[27–29] To classify the SUDEP cases, we used the Annegers classification[30]:

Definite SUDEP: cases meet all criteria and have sufficient descriptions of the circumstances of the death, with postmortem examination.

Probable SUDEP: cases meet all criteria, but lack postmortem data.

Possible SUDEP: cases in which SUDEP cannot be ruled out, but there is insufficient evidence regarding the circumstances of the death and no postmortem report available.

Statistical analysis

For comparison between the two groups, an independent sample t-test was used. Univariate Cox regression analysis was performed to identify baseline variables associated with all-cause mortality and SUDEP. In the SUDEP analysis, the endpoint was defined as definite/probable SUDEP and patients were censored at time of death if death was due to another cause than SUDEP or at the end of the study. HRs with corresponding 95% CI were calculated. Forward stepwise multivariable logistic regression was conducted for baseline and follow-up variables with $p<0.10$ in the univariate analysis. Two-sided p value<0.05 was considered significant.

Statistical analysis was performed using IBM SPSS Statistics V.26 and SAS V.9.4.

RESULTS

Baseline variables

We identified 1329 patients who had undergone resective epilepsy surgery and 666 patients who were evaluated for surgery but not operated. The total follow-up time was 31 161 person-years. Baseline data for the two cohorts are shown in table 1.

The proportion of children was higher in the surgical group, and patients in the non-surgical group were slightly older. The operated patients with TCS had a mean of 17.2 (SD 79.7) TCS per month, and the non-operated patients had a mean of 7.8 (SD 25.2) TCS per month. Temporal lobe resection was the most common resection, followed by frontal lobe resection. Mean follow-up time (from surgery to last follow-up) was 9.1 years (SD 6.7). In the non-surgical group, there was information on reasons for not proceeding to surgery only for 224 patients. The most common reasons were inconclusive investigation (35%) and multifocal epilepsy (20%).[24]

Table 1 Baseline data

	Surgical group	Non-surgical group
Patients, n (%)	1329 (66.6)	666 (33.3)
Age at inclusion (years)	27.2 (0.2–74.9)	30.1 (1.2–70.7)
<18 years, n (%)	431 (32.4)	123 (18.5)
Age at epilepsy onset (years)	12.2 (0–58.0)	14.0 (0–57.0)
Duration of epilepsy (years)	13.3 (0–57.0)	15.4 (0–63.0)
Male, n (%)	670 (50.9)	328 (49.2)
Repeated surgery, n (%)	164 (12.3)	NA
Seizures/month		
Mean, median (range)	70.1, 12.0 (0.1–10 000)	34.6, 8.0 (0.1–1600)
0–5, n (%)	387 (30)	216 (39)
6–20, n (%)	436 (33)	186 (34)
>20, n (%)	492 (37)	152 (27)
TCS, n (%)	531 (40.0)	268 (47.4)
Living alone*, n (%)	227 (26.0)	142 (30.1)
Highest achieved education†, n (%)		
University	113 (12.8)	77 (16.5)
High school	422 (47.6)	222 (47.5)
Compulsory school	295 (33.3)	153 (32.8)
Adapted schooling for students with ID	56 (6.3)	15 (3.2)
Total number of tried ASMs, n (%)		
≤2 ASM	295 (22.2)	42 (9.4)
≥3 ASM	1031 (77.8)	407 (90.6)
Type of resection, n (%)		
Temporal lobe	874 (65.8)	NA
Frontal lobe	240 (18.1)	NA
Parietal, occipital lobe or insula	106 (7.9)	NA
Multilobar resection	48 (3.5)	NA
Hemispherectomy	44 (3.3)	NA
Disconnection of hypothalamic hamartoma	17 (1.3)	NA
Histopathology, n (%)		
LEATs, meningioma and cavernous hemangioma	337 (25.4)	NA
Mesial sclerosis and other gliosis	514 (38.7)	NA
Any malformation of cortical development	290 (21.8)	NA
Other, including AVM	121 (9.1)	NA
Missing/not performed/normal	67 (5.0)	NA
Last follow-up timepoint, n (%)		
2 years	391 (32.1)	NA
5 years	215 (17.7)	NA
10 years	206 (16.9)	NA
15 years	204 (16.7)	NA
20 years	202 (16.6)	NA

Unless otherwise indicated, data are presented as mean (range).
The subgrouping of variables for seizure frequency and ASM is arbitrary for descriptive purposes only.
LEATs=ganglioglioma, dysembryoplastic neuroepithelial tumour, pleomorphic xanthoastrocytoma grade II, oligodendroglioma grade II, pilocytic astrocytoma, diffuse astrocytoma grade II and neurocytoma.
*Children<18 years excluded.
†Children 0–16 years excluded.
ASM, antiseizure medication; AVM, arteriovenous malformation; ID, intellectual disabilities; LEATs, long-term epilepsy-associated tumours; TCS, tonic–clonic seizures.

Last follow-up for operated patients

Figure 2A,B shows seizure outcome at last follow-up. Among patients with persistent seizures, mean seizure frequency per month was 36.8 (SD 130.7), median 4.0 (range 0.1–1250.0). Mean TCS frequency per month in patients with TCS was 10.4 (SD 43.2), median 1.0 (range 0.1–500.0). Of the patients>18 years, 215 (21.3%) were living alone. Reasons for not being followed-up were 2-year follow-up planned after study end

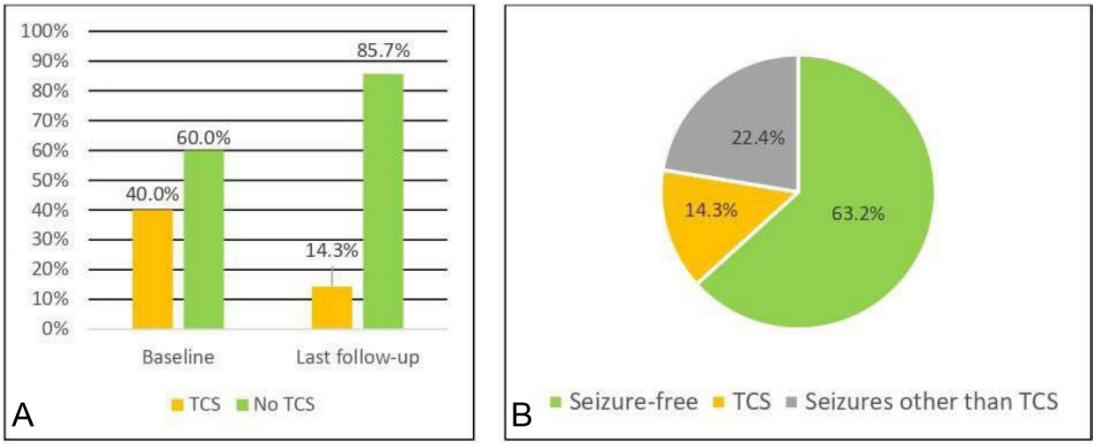

Figure 2 (A) Presence of TCS for operated patients at baseline and at last follow-up. (B) Seizure outcome for operated patients, at last follow-up. TCS, tonic–clonic seizures.

(n=66), death before 2 year-follow-up (n=14) and lost to follow-up (n=31).

Mortality

During the period, 132 (9.9%) operated patients and 79 (11.9%) non-operated patients died. This corresponds to 6.0 vs 8.7 deaths per 1000 person-years. Operated patients had lower all-cause mortality compared with non-operated patients (p=0.0052) (figure 3). Causes of death are shown in table 2. The most common cause of death was SUDEP in both groups. There were 15 deaths due to accidents of which 10 (5 in each group) were drowning accidents. The autopsy reports indicated that an epileptic seizure could have contributed in the latter cases. There were two accidents with missing information and three traumatic falls probably related to seizures. This corresponds to 1.82 SUDEP cases/1000 person-years and 0.23 death accidents/1000 person-years in the surgical group, and 2.40 SUDEP cases/1000 person-years and 0.87 death accidents/1000 person-years in the non-surgical group. For operated patients with persisting seizures, the SUDEP incidence rate was 0.24 SUDEP cases/1000 person-years and for seizure-free patients 0.07 SUDEP cases/1000 person-years.

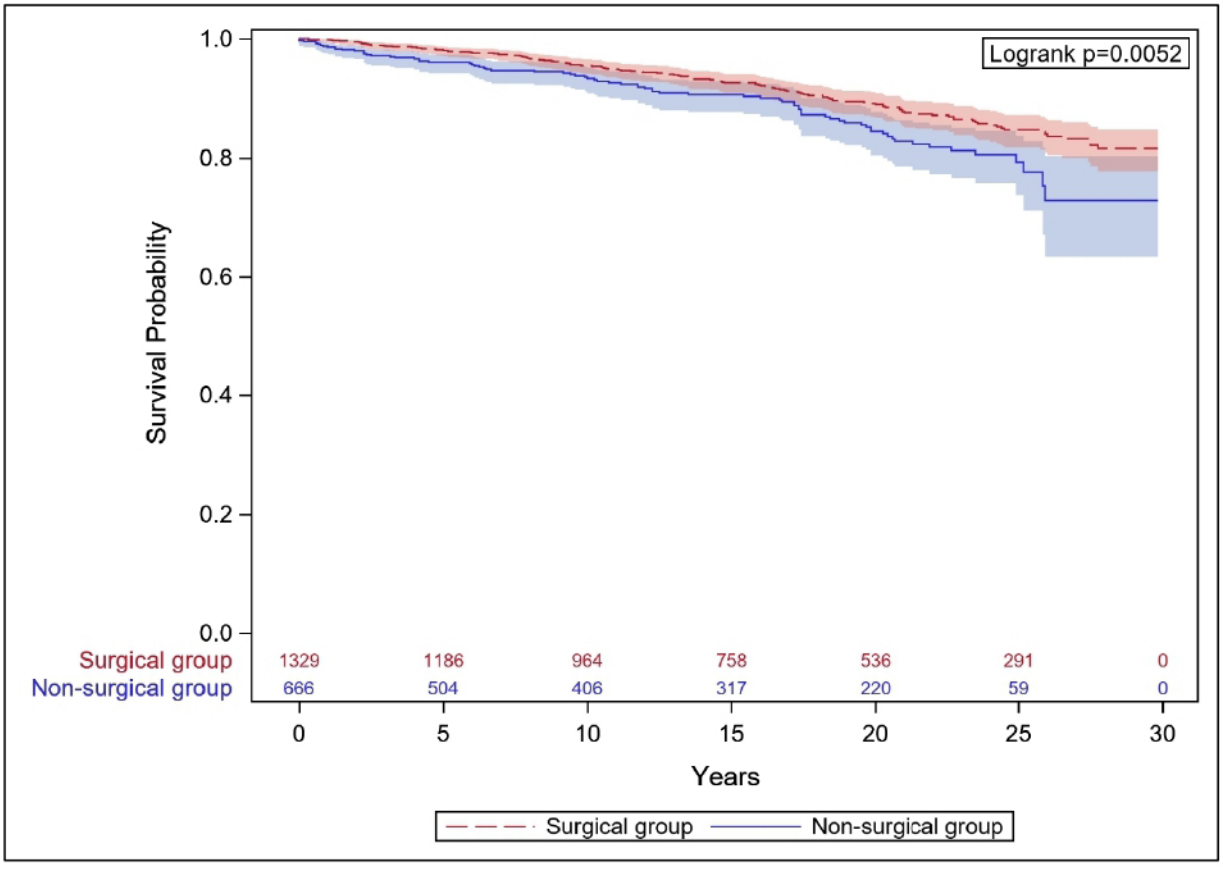

Figure 3 The Kaplan-Meier curve showing survival probability in operated and non-operated patients.

Table 2 Causes of death

Cause of death, n (%)	Female, operated	Male, operated	All, operated	Female, non-operated	Male, non-operated	All, non-operated
All SUDEP	19 (33.3)	21 (28)	40 (30.3)	8 (22.2)	14 (32.6)	22 (27.8)
Definite SUDEP	12 (21)	18 (24)	30 (22.7)	6 (16.7)	11 (25.6)	17 (21.5)
Probable SUDEP	7 (12.5)	3 (4)	10 (7.6)	2 (5.6)	3 (7)	5 (6.3)
Cancer (brain tumours excluded)	12 (21.1)	10 (13.3)	22 (16.7)	7 (19.4)	5 (11.6)	12 (15.2)
Cardiovascular disease	6 (10.5)	15 (20)	21 (15.9)	6 (16.7)	8 (18.6)	14 (17.7)
Brain tumour	8 (14)	6 (8)	14 (10.6)	5 (13.9)	1 (2.3)	6 (7.6)
Infection	4 (7)	3 (4)	7 (5.3)	0 (0)	3 (7)	3 (3.8)
Status epilepticus	0 (0)	2 (2.7)	2 (1.5)	0 (0)	1 (2.3)	1 (1.3)
Suicide	1 (1.8)	6 (8)	7 (5.3)	2 (5.6)	0 (0)	2 (2.5)
Accident (including drowning)	0 (0)	5 (6.7)	5 (3.8)	4 (11.1)	4 (9.3)	8 (10.1)
Other*	7 (12.3)	7 (9.3)	14 (10.6)	4 (11.1)	7 (16.3)	11 (13.9)
Total	57 (43.2)	75 (56.8)	132 (100)	36 (45.6)	43 (54.4)	79 (100)

*The category 'other' included six pulmonary diseases, four unknown diagnosis, three gastrointestinal diseases, three intoxications (non-suicide), two epilepsy surgery complications, two kidney diseases, one multiple sclerosis, one dementia, one aspiration, one anaphylaxis and one alcoholism.
SUDEP, sudden unexpected death in epilepsy.

Mean age at death was 48 years (range 3–86) in the surgical group and 46 years (range 5–86) in the non-surgical group (p=0.35). Patients who died of SUDEP had a mean age of 37 years compared with 52 years in the group with all other causes of death (p<0.001).

Predictors for all-cause mortality and SUDEP

Baseline variables investigated as predictive factors for all-cause mortality for all patients are presented in table 3. In univariate analysis, surgery was associated with a lower risk of all-cause mortality, whereas higher age, longer epilepsy duration and TCS at baseline were associated with an increased risk. TCS at baseline was the only significant predictor for SUDEP. In the multivariable model, the operated patients had a reduced risk of mortality independently of age, gender, TCS at baseline and epilepsy duration.

Prediction analyses of follow-up variables for operated patients are shown in table 4. Continuing seizures, TCS, higher age and living alone at last follow-up increased the risk for all-cause death in both univariate and multivariable analyses. Seizure outcome was the only predictor of SUDEP.

DISCUSSION

In this study, we investigated mortality in a large, population-based cohort of adults and children who had undergone epilepsy surgery and in a large group of non-operated drug-resistant

Table 3 Univariate and multivariable analysis of baseline predictors for all-cause mortality and SUDEP for all patients

	All-cause mortality		SUDEP	
Univariate Cox regression analysis	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.04 (1.03 to 1.05)	**<0.001**	1.00 (0.99 to 0.02)	0.72
Duration of epilepsy (years)	1.02 (1.01 to 1.03)	**0.001**	1.01 (0.99 to 1.03)	0.27
Male sex	1.26 (0.96 to 1.66)	0.09	1.29 (0.78 to 2.14)	0.31
Surgery	0.67 (0.51 to 0.89)	**0.006**	0.78 (0.47 to 1.32)	0.36
TCS	1.42 (1.078 to 1.87)	**0.013**	2.51 (1.48 to 4.27)	**0.001**
Living alone*	1.01 (0.72 to 1.41)	0.95	0.99 (0.52 to 1.87)	0.97
Highest education†				
University (ref)	1	1	1	1
High school	0.82 (0.51 to 1.32)	0.42	0.80 (0.34 to 1.89)	0.61
Compulsory school	1.04 (0.65 to 1.66)	0.89	0.87 (0.36 to 2.11)	0.76
Adapted schooling for students with ID	0.91 (0.43 to 1.92)	0.81	0.63 (0.13 to 3.06)	0.57
Tried>3 ASM	0.91 (0.64 to 1.29)	0.59	1.30 (0.64 to 2.65)	0.46

	All-cause mortality	
Multivariable Cox regression analysis‡	HR (95% CI)	P value
Age (years)	1.04 (1.03 to 1.05)	**<0.001**
Male	1.41 (1.06 to 1.87)	**0.019**
Surgery	0.67 (0.49 to 0.91)	**0.010**

Bold values denote statistical significance at the p < 0.05 level.
*Children<18 years excluded.
†Children 0–16 years excluded.
‡TCS and duration of epilepsy were not included in the final multivariable model (removed by the model).
ASM, antiseizure medication; ID, intellectual disability; SUDEP, sudden unexpected death in epilepsy; TCS, tonic–clonic seizures.

Table 4 Univariate and multivariable analysis of predictors for all-cause mortality and SUDEP for operated patients

	All-cause mortality		SUDEP	
Univariate Cox regression analysis	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Male	1.25 (0.89 to 1.77)	0.20	1.06 (0.57 to 1.97)	0.86
Age (years)	1.05 (1.03 to 1.06)	**<0.001**	1.01 (0.99 to 1.04)	0.21
Repeat surgery	1.22 (0.72 to 2.10)	0.46	0.88 (0.37 to 2.11)	0.78
Non-LEATs*	1.04 (0.70 to 1.56)	0.85	1.84 (0.77 to 4.38)	0.17
Seizure outcome at last follow-up				
Seizure free (ref)	1	1	1	1
TCS	1.77 (1.07 to 2.92)	**0.025**	4.61 (2.03 to 10.44)	**<0.001**
Seizures other than TCS	2.25 (1.49 to 3.41)	**<0.001**	2.83 (1.23 to 6.54)	**0.015**
Living alone at last follow-up†	1.60 (1.09 to 2.36)	**0.016**	1.45 (0.70 to 2.98)	0.32
Non-temporal lobe resection	1.32 (0.90 to 1.94)	0.16	1.65 (0.79 to 3.47)	0.19

	All-cause mortality	
Multivariable Cox regression analysis	**HR (95% CI)**	**P value**
Age (years)	1.05 (1.03 to 1.06)	**<0.001**
Seizure outcome at last follow-up		
Seizure free (ref)	1	1
TCS	1.78 (1.07 to 2.96)	**0.027**
Seizures other than TCS	2.14 (1.41 to 3.23)	**<0.001**
Living alone at last follow-up†	1.47 (1.01 to 2.13)	**0.045**

Bold values denote statistical significance at the $p < 0.05$ level.
LEATs=ganglioglioma, dysembryoplastic neuroepithelial tumour, pleomorphic xanthoastrocytoma grade II, oligodendroglioma grade II, pilocytic astrocytoma, diffuse astrocytoma grade II and neurocytoma.
*Reference LEATs, meningioma and cavernous hemangioma.
†Children<18 years excluded.
LEATs, long-term epilepsy-associated tumours; SUDEP, sudden unexpected death in epilepsy; TCS, tonic–clonic seizures.

patients evaluated for surgery. The surgical group showed a 50% reduction in seizure frequency and 63% of all operated patients were seizure free at their last follow-up. Epilepsy surgery independently decreased the mortality risk. Around 40% of the deaths were epilepsy related with SUDEP being the most common cause of death in both groups, accounting for one-third of all deaths. Seizure freedom was associated with a lower risk of both all-cause mortality and SUDEP. There were more patients per 1000 person-years who died of SUDEP or accidents (where an epileptic seizure might have contributed) in the non-surgical group compared with the surgical group, although this was not significant in the Cox regression analysis. The majority of previous studies have shown similar results concerning mortality. No study has shown unequivocal results regarding SUDEP after surgery.[16 18–20 22 23 31] Several studies were small, one had no comparison group and the SUDEP numbers were below 20. A large Swedish case–control study on SUDEP could not confirm epilepsy surgery to be protective for SUDEP but included few operated patients.[9] A recent meta-analysis on studies of mortality after epilepsy surgery, calculated a mortality rate of 6.14 per 1000 person-years for the operated patients, and an OR of 0.40 for incidence of death in operated compared with non-operated patients.[23] This mortality rate is on par with our results. Although the meta-analysis comprised almost 10 000 patients, follow-ups were shorter. The number of person-years in the meta-analysis (34 500) is quite comparable to our study (31 000). The decreased mortality after surgery seemed to persist and possibly increase after 15 years. Given that the majority of operated patients are young, it is reasonable to assume that this effect may last even longer. Large longer-term multicentre cohort studies are warranted in order to investigate this further. Persisting seizures at follow-up, in particular TCS, was the only identified predictor of SUDEP in the surgical group. In contrast to the Swedish case–control study,[9] we also found an association between SUDEP and non-TCS, although it was less pronounced than for TCS. Moreover, non-TCS was a risk factor for all-cause mortality in the surgical group. A non-significant indication of such a relationship was also found in one earlier, smaller study.[16] One possibility might be that focal seizures with impaired awareness increase the risk for epilepsy related fatal accidents. Also, the incidence of epilepsy-related fatal accidents was higher for the non-operated patients. Furthermore, earlier studies have shown a higher frequency of ictal apnoea and asystole in focal temporal lobe seizures, which might contribute to SUDEP in the non-TCS patients.[11 32–34] For operated patients, living alone at last follow-up was a risk factor for all-cause mortality. This is in line with studies that have demonstrated lower mortality rates after cardiovascular disease for those who live with others.[35 36] An association between living alone and SUDEP has been found in two earlier studies investigating mortality in individuals with epilepsy.[9 37] However, our study could not confirm such an association, even though the HR for living alone and SUDEP approached that of all-cause mortality. One explanation might be that our study dichotomised between living alone or not, whereas the earlier studies took other aspects into account such as supervision or shared bedroom. The operated patients had higher seizure frequency, including TCS, compared with non-operated patients at baseline. This could indicate a more severe and complex epilepsy and potentially a higher mortality risk at baseline. If this is the case, the results of this study might actually be an underestimation of the difference in mortality risk between the two groups.

The strengths of this population-based study include the large cohorts of operated and non-operated patients, the long follow-up time and the completeness of mortality data. Our study comprises all resective epilepsy surgery procedures in

Sweden since 1990 with a follow-up time of more than 10 years for the majority of the patients. The number of person-years in our study (31 161) is on par with the sum of all studies included in a recent meta-analysis.[23] We used overlapping sources to find causes of death and to identify SUDEP, including discussions with a pathologist. There were also limitations to this study. The number of SUDEP cases may have been underestimated since the autopsy frequency is decreasing. Only 11% of deaths underwent clinical or forensic autopsy in Sweden in 2016.[38] Reasons for not being operated were available for only one-third of the non-operated patients, but differences concerning the area of seizure onset and network spread, which most probably affect outcome, can be assumed at least for some of them.[24] Follow-up data on seizure status and living conditions was not available for non-operated patients, which precluded analyses of how these factors relate to patient survival. In summary, our study confirmed that operated patients have lower mortality over time than non-operated patients with drug-resistant epilepsy. Two-thirds of the operated patients reported seizure freedom at their last follow-up, which predicted an even lower risk of mortality and SUDEP. Epilepsy surgery is still an underused treatment option. The results of this study further emphasise the importance of considering epilepsy surgery for patients with drug-resistant epilepsy.

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Ethics approval This study involves human participants. This study was approved by the Regional Board of Medical Ethics at the University of Gothenburg, EPN 078-09, T679-10 and T1136-18. As the study is register based, the Regional Board of Medical Ethics at the University of Gothenburg waived the requirement to obtain individual informed consent.

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ORCID iD

Cecilia Granthon http://orcid.org/0009-0006-7025-3048

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