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Epidemiology, healthcare resource use, and mortality in patients with probable Lennox-Gastaut syndrome: A population-based study on German health insurance data

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ABSTRACT

Objective: This retrospective study examined patients with probable Lennox-Gastaut syndrome (LGS) identified from German healthcare data.
Methods: This 10-year study (2007–2016) assessed healthcare insurance claims information from the Vilua Healthcare research database. A selection algorithm considering diagnoses and drug prescriptions identified patients with probable LGS. To increase the sensitivity of the identification algorithm, two populations were defined: all patients with probable LGS (broadly defined) and only those with a documented epilepsy diagnosis before 6 years of age (narrowly defined). This specific criterion was used as LGS typically has a peak seizure onset between age 3 and 5 years. Primary analyses were prevalence and demographics; secondary analyses included healthcare costs, hospitalization rate and length of stay (LOS), medication use, and mortality.
Results: In the final year of the study, 545 patients with broadly defined probable LGS (mean [range] age: 31.4 [2–89] years; male: 53%) were identified. Using the narrowly defined probable LGS definition, the number of patients was reduced to 102 (mean [range] age: 7.4 [2–14] years; male: 52%). Prevalence of broadly defined and narrowly defined probable LGS was 39.2 and 6.5 per 100,000 people. During the 10-year study, 208 patients with narrowly defined probable LGS were identified and followed up for 1379 patient-years. The mean annual cost of healthcare was €22,787 per patient-year (PPY); greatest costs were attributable to inpatient care (33%), home nursing care (13%), and medication (10%). Mean annual healthcare costs were significantly greater for those with prescribed rescue medication (45% of patient-years) versus those without (€33,872 vs. €13,785 PPY, $p < 0.001$). Mean (standard deviation [SD]) annual hospitalization rate was 1.6 (2.0) PPY with mean (SD) annual LOS of 22.7 (46.0) days. Annual hospitalization rate was significantly greater in those who were prescribed rescue medication versus those who were not (2.2 [2.3] vs. 1.1 [1.6] PPY, $p < 0.001$). The mean (SD) number of different medications prescribed was 11.3 (7.3) PPY and 33.8 (17.0) over the entire observable time per patient (OET); antiepileptic drugs only accounted for 2.1 (1.1) of the medications prescribed PPY and 3.8 (2.0) OET. Over the 10-year study period, mortality in patients with narrowly defined probable LGS was significantly

Abbreviations: AED, antiepileptic drug; AHR, annual hospitalization rate; ATC, Anatomical Therapeutic Chemical Classification System; CI, confidence interval; DS, Dravet syndrome; GKV, Gesetzliche Krankenversicherung (statutory health insurance); ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome; LOS, length of stay; OET, over the entire observable time per patient; PPY, per patient-year; Q, quarter; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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higher than the matched control population (six events [2.88%] vs. one event [0.01%], $p < 0.001$).
Conclusion: Annual healthcare costs incurred by patients with probable LGS in Germany were substantial, and mostly attributable to inpatient care, home nursing care, and medication. Patients prescribed with rescue medication incurred significantly greater costs than those who were not. Patients with narrowly defined probable LGS had a higher mortality rate versus control populations.

1. Introduction

Lennox-Gastaut syndrome (LGS) is a polyetiological, predominantly childhood-onset, severe developmental epileptic encephalopathy associated with high morbidity and mortality, with an estimated prevalence rate of 1–10% of all childhood epilepsies [1–5]. Treatment options for LGS are limited and long-term prognosis is poor [5]. No single treatment approach has been shown to be highly efficacious and many patients receive polypharmacy without adequate seizure control [5,6]. The management of LGS is further complicated by its associated comorbidities, especially cognitive impairment and behavioral problems, and the variety of different seizure types that characterize the syndrome [1,4]. Such complexity can make it difficult to tailor therapeutic approaches to those without a clearly defined and treatable etiology.

The burden of LGS is multifaceted and extends beyond the availability of adequate treatment; seizure burden is typically quantified using seizure frequency but this gives limited scope for understanding the breadth of impact [7]. The implications of the syndrome can be wide-ranging: patients often experience mobility or behavioral impacts, while families/caregivers can experience limited career opportunities [8]. Furthermore, patients and their families/caregivers can be exposed to decreased social participation [8,9]. The high cost of treatment and necessity for long-term care can exacerbate these negative effects and create further stress for those living with the burden of LGS [8–10].

Healthcare cost and utilization data offer an opportunity to quantify some of the burden associated with medical conditions and may provide insight that can change treatment approaches and improve patient care [11]. Currently, there is a lack of such analyses for LGS and other epileptic encephalopathies, particularly for pediatric patients [12].

The general lack of healthcare cost and utilization data for LGS is most likely due to its low prevalence and different underlying etiologies, and a lack of appropriately captured healthcare information in medical records/databases. Furthermore, the International Classification of Diseases, 10th Revision (ICD-10) did not include a specific code for LGS. The future release of ICD-11 (scheduled for 2022) will include a code for LGS (8A62.1 Lennox-Gastaut syndrome), although it is believed that widespread adoption and implementation of the code could take at least another decade, and perhaps even longer, to yield data for research. In the meantime, the need for healthcare utilization and cost analyses in LGS is beginning to be addressed using patient selection algorithms to identify patients with probable LGS using ICD-10 data.

The few published healthcare utilization studies in patients with LGS have all reviewed healthcare data from patients based in the USA (Medicaid and MarketScan® databases) [6,11,13,14]. Since all previous studies have used an algorithm to detect the patients most likely to have been diagnosed with LGS, all studies refer to patients with 'probable LGS'. The algorithm used was highly consistent between these studies [6,11,13,14]. As noted previously, LGS is a predominantly childhood-onset syndrome, most commonly manifesting itself between ages 3–5 years [4], yet no previous study has included a maximum age cut-off for the first diagnosis of epilepsy as an indicator for probable LGS.

The objective of this retrospective study was to examine epidemiology, healthcare cost and utilization, medication use, comorbidities, injuries, and mortality for patients with LGS. Using information from a German healthcare insurance claims database, this study is the first to present these analyses for patients with LGS based in Europe.

2. Materials and methods

2.1. Data source

This study utilized healthcare insurance claims data obtained from the Vilua Healthcare research database, which contains entries for >4 million individuals, and represents approximately 5% of the German population covered by statutory health insurance (Gesetzliche Krankenversicherung; GKV). The database is continuously evaluated to ensure that it is comparable to the German population by comparison to the annual publications of the German Federal Office for Social Security (Bundesamt für Soziale Sicherung) and has been used previously for epidemiological studies in epilepsy, status epilepticus, and multiple sclerosis [15–18]. All data obtained from this database were de-identified; entries were routinely inspected for outliers, data errors, and longitudinal changes. Analyses of these data were approved by the ethics committee of the University of Frankfurt and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [19].

2.2. Identification of patients with probable Lennox-Gastaut syndrome

In the Vilua Healthcare research database, there was no option to select specifically for those diagnosed with LGS due to the absence of an LGS-specific diagnosis code in the ICD-10 classification system. All ICD codes used for this study are listed in Appendix Table S1.

To account for the lack of an ICD code for LGS, and to retrieve those patients most likely to have a diagnosis of LGS, while also excluding those with other neurological disorders, an identification algorithm considering diagnoses and drug prescriptions was defined (Fig. 1). This selected patients with $\geq$1 ICD-10 diagnosis of G40 (epilepsy)/G41 (status epilepticus) and $\geq$1 claim of either rufinamide or felbamate (during the year of identification). If there was no claim of rufinamide or felbamate, $\geq$2 different antiepileptic drugs (AEDs) in combination with $\geq$1 developmental delay diagnosis and no diagnosis code for competing etiologies were required (also during the year of identification; ICD codes are listed in Appendix Table S1). For example, those with an ICD-10 code for malignant neoplasms were excluded on the basis of competing etiology. Patients with probable Dravet syndrome (DS) were excluded from the present study population using a DS-specific algorithm based on diagnosis of epilepsy and prescription of certain AEDs that was defined for a separate analysis. Patients with tuberous

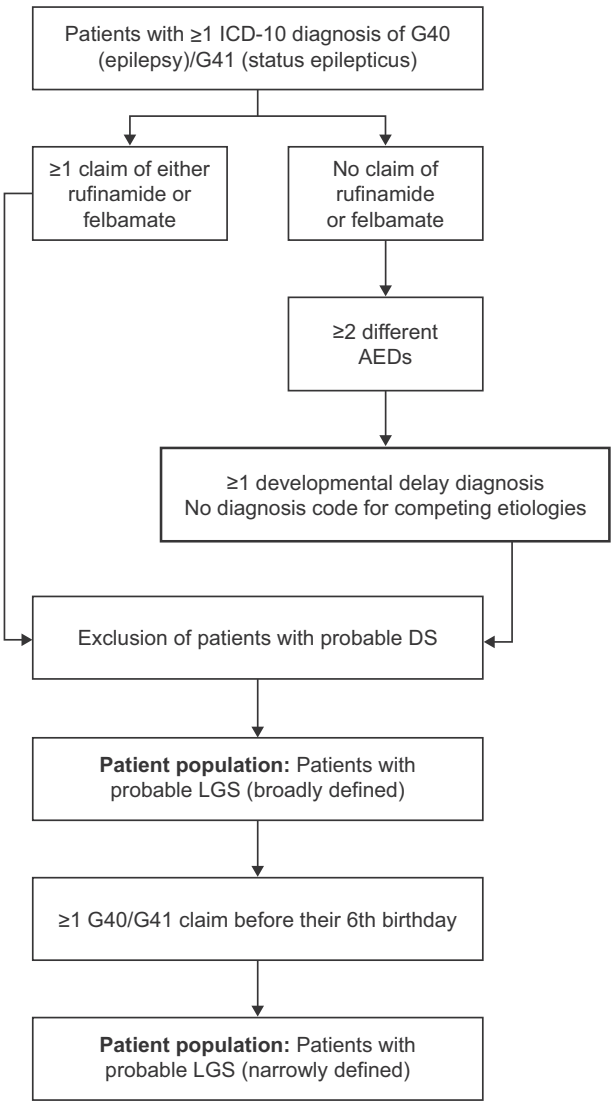

Fig. 1. Patient selection process for probable LGS. AED, antiepileptic drug; ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome.

sclerosis complex (TSC) were also excluded and are part of a separate analysis.

To increase the sensitivity of the identification algorithm, two populations were defined: all patients with probable LGS (broadly defined probable LGS) and only those with ≥1 documented G40/G41 claim before their 6th birthday (narrowly defined probable LGS). Patients aged 6 years or older on the first day of the study could not be included in the narrowly defined LGS population. The selection of those with ≥1 G40/G41 claim prior to age 6 was informed by previous literature; LGS typically presents before age 8, with peak seizure onset between age 3 and 5 [4]. The stratification of patients with probable LGS based on this additional criterion increased the sensitivity (true-positive rate) of the study.

2.3. Outcomes

Data from a 10-year period between January 1, 2007 and December 31, 2016 were assessed. The primary analyses were prevalence, and age and sex distribution in the two populations: broadly defined and narrowly defined probable LGS. These analyses were calculated using the number of patients identified in the final year of the study (2016); the final year was chosen because coding quality improved from study onset (2007) through to completion (2016) and so presenting the final year data ensured the highest possible reporting accuracy. Furthermore, with 2016 being the final year, it also allowed the study to present the most recent epidemiological data available. Secondary analyses were annual healthcare costs, annual hospitalization rate and length of stay (LOS, measured in days; all patients, patients hospitalized due to primary probable LGS diagnosis, and patients hospitalized with mechanical ventilation), medication use, comorbidities, injuries, and mortality. Secondary analyses were assessed using the number of patients identified across the entire study (2007–2016) and were only conducted in the narrowly defined probable LGS population. All analyses, apart from prevalence, were based on fully observable patients, defined as those whose data were available for the complete observation year in question. Annual healthcare costs were stratified by age group (0–1, 2–9, and 10–19 years); given that most AEDs are only approved for use in patients with LGS ≥1 year of age, it was of interest to evaluate costs in younger patients.

Previous analyses have suggested a lower age of seizure onset, increased frequency of seizures, and an increased number of prescribed AEDs in patients with rescue medication use versus those with no rescue medication use [20]. To explore this further, subgroup analyses of cost, hospitalization rate, LOS, and mortality data were conducted based on prescription of rescue medication, defined as at least one prescription of midazolam, diazepam (rectal formulation), or chloral hydrate in at least 1 year during the study period.

The cost of illness associated with probable LGS was assessed using a top-down approach, from the perspective of the statutory health insurer. This approach was applied to all hospitalization admissions within the specified analysis period. Cost data by age were evaluated over a 10-year period; within this, costs were recorded annually according to age at the time of assessment. All costs were calculated in Euros (€) and were adjusted to the 2015 price year using the German Health Consumer Price Index [21]. LOS at discharge was calculated using the database. The number of different medications was determined from the number of different Anatomical Therapeutic Chemical Classification System (ATC) codes noted throughout the study for a particular patient. The most commonly prescribed AEDs (ATC code N03A + clobazam) were assessed using the data for each patient in their last observation year; this was either the final year of the study or the year in which the patient left the database (for example, the patient may have switched to another insurance company, left the country, or died). Injury and mortality were compared to age- and sex-matched (standardized) controls over an equal observation time. To generate these controls, the database was searched for as many patients as possible who did not have a diagnosis of probable LGS, probable DS, or TSC and were of the same age and sex, and with at least an equal observation time, as the patient with probable LGS.

2.4. Statistical analysis

All data were analyzed with SQL Server 2016 SP2, R 3.5.0 and Microsoft Excel. *P*-values were derived from a *t*-test hypothesizing that the mean costs (per setting) of the patients with prescribed rescue medication were equal to the mean costs (per setting) of the patients with no prescribed rescue medication. *P*-values were also derived from a log rank test (using chi-squared distribution) to assess the significance of mortality data versus standardized controls.

3. Results

3.1. Patient demographics and characteristics

Using data from the final year of this 10-year study (2016), the classification algorithm identified 545 patients with broadly defined probable LGS, of whom 102 (19%) fulfilled the criteria for narrowly defined probable LGS (Table 1). During the 10-year study, 1571 patients with broadly defined probable LGS were identified and followed up for 12,090 patient-years; 208 patients with narrowly defined probable LGS were identified and followed up for 1379 patient-years.

Using data from 2016, the prevalence (age and sex standardized to German GKV population) of broadly defined and narrowly defined probable LGS was 39.2 and 6.5 per 100,000 people. The mean (range) age was 31.4 (2–89) years in the broadly defined and 7.4 (2–14) years in the narrowly defined population. The narrowly defined population included only those patients for whom the initial epilepsy diagnosis took place within the overall study period (2007–2016); thus, the oldest patient in this population was 14 years old on the final day of study (<6 years of age on the first day of study). Sex distribution (% male) was similar in the broadly defined (53%) and narrowly defined (52%) populations and was consistent across all age groups in both populations.

During the 10-year study period, almost all (178/208, 86%) patients in the narrowly defined probable LGS population were prescribed rescue medication at some point during the follow-up period.

3.2. Healthcare costs

All cost analyses were conducted using the narrowly defined probable LGS population (n = 208; 1379 patient-years).

3.2.1. All patients

During the 10-year study period, the mean annual cost of healthcare was €22,787 per patient-year (Table 2). The greatest contributors to healthcare costs were inpatient care (33%), home intensive nursing care/nursing care (13%), and medication (10%). Inpatient costs resulting from hospital stays related to epilepsy were high (€5636 per patient-year). However, AEDs alone accounted for a small proportion (14%) of the medication costs. High non-AED medication costs were influenced by several expensive medications that were prescribed to a small number of patients over the study period, for example anterior pituitary lobe hormones and analogs to one patient (total of three prescriptions at a mean cost of €3642 per prescription), systemic antimycotics to two patients (four prescriptions, €1823), and immunoglobulins to seven patients (31 prescriptions, €1215).

3.2.2. Patients with prescribed rescue medication

During the 10-year study period, the mean annual cost of healthcare was significantly greater for those prescribed with rescue medication (patient-years in which patients received rescue medication: 618/1379, 45%) versus those not (€33,872 vs. €13,785 per patient-year, $p < 0.001$; Table 2). Similar to the overall population, inpatient care was the largest component of the total costs and was significantly greater for patients with prescribed rescue medication than those without. Costs for home nursing, special equipment, and other physical therapies were markedly and significantly greater in patients with prescribed rescue medication than those without. Medication costs comprised 10% of overall costs in the prescribed rescue medication subgroup and 9% in the subgroup not prescribed rescue medication; the proportions of these costs associated with AEDs were equivalent in both subgroups (14%). In those prescribed rescue medication, mean annual cost per patient-year was greatest in the 0- to1-year age category (€53,073 per patient-year); costs were similar between the 2- to 9-year and 10- to 19-year age categories (€31,614 and €33,030 per patient-year). Higher costs in the 0- to 1-year age category were mostly attributable to inpatient care (€26,369 vs. €7976 and €7817 per patient-year in the 2- to 9-year and 10- to 19-year categories, respectively).

Table 1
Epidemiology of patients with probable LGS (broadly and narrowly defined) in 2016.

	Patients identified with probable LGS			
	Broadly defined		Narrowly defined	
No. of patients, n (%)	545 (100)		102 (19)	
Mean age, years	31.4		7.4	
Prevalence[a] (per 100,000 people)				
Unstandardized to the German GKV population	41.1		7.7	
Standardized to the German GKV population	39.2		6.5	
Sex distribution per age group, n (%)				
Age range (years)	Male	Female	Male	Female
0–1	0 (0)	0 (0)	0 (0)	0 (0)
2–9	40 (14)	37 (15)	39 (74)	34 (69)
10–19	56 (19)	71 (28)	14 (26)	15 (31)
20–29	53 (18)	36 (14)	0 (0)	0 (0)
30–39	38 (13)	31 (12)	0 (0)	0 (0)
40–49	38 (13)	18 (7)	0 (0)	0 (0)
50–59	35 (12)	31 (12)	0 (0)	0 (0)
60–69	22 (8)	17 (7)	0 (0)	0 (0)
70–79	7 (2)	10 (4)	0 (0)	0 (0)
80+	2 (1)	3 (1)	0 (0)	0 (0)

GKV, Gesetzliche Krankenversicherung (statutory health insurance); LGS, Lennox-Gastaut syndrome.

[a] Prevalence calculations are based on all patients, including those who changed insurance company or died during an observation year (patients identified with probable LGS [broadly defined], n = 553; patients identified with probable LGS [narrowly defined], n = 104); all other analyses are based on fully observable patients only i.e. those whose medical data were available across the entire observation year in question (patients identified with probable LGS [broadly defined], n = 545; patients identified with probable LGS [narrowly defined], n = 102).

Table 2
Summary of cost data, including stratification into patient groups with/without prescription of rescue medication[a] for patients with narrowly defined probable LGS during the 10-year study period.

	All patients	Years where patients prescribed with rescue medication[a]	Years where patients not prescribed with rescue medication[a]	*p*-value[b]
Annual cost per patient-year, €				
Patient-years	1379	618	761	
Total				
Mean	22,787	33,872	13,785	<0.001
Median (Q1–Q3)	4439 (0–18,489)	11,897 (0–30,500)	2058 (0–9120)	
Inpatient				
Mean	7422	9776	5511	0.001
Median (Q1–Q3)	0 (0–5394)	1427 (0–10,628)	0 (0–1947)	
Epilepsy-related				
Mean	5636	8336	3288	<0.001
Median (Q1–Q3)	0 (0–5243)	2580 (0–8814)	0 (0–2008)	
Outpatient				
Mean	1390	1826	1036	<0.001
Median (Q1–Q3)	708 (0–1681)	1122 (0–2005)	388 (0–1336)	
Medication				
Mean	2243	3479	1240	<0.001
Median (Q1–Q3)	427 (0–1991)	1126 (0–3797)	146 (0–971)	
AEDs				
Mean	309	483	169	<0.001
Median (Q1–Q3)	100 (0–354)	225 (17–576)	0 (0–196)	
Services and devices				
Mean	11,731	18,791	5997	<0.001
Median (Q1–Q3)	703 (0–5282)	2310 (0–11,327)	27 (0–2256)	
Intensive home nursing care				
Mean	1971	3479	746	0.018
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Special equipment				
Mean	1309	2316	490	<0.001
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Home nursing care				
Mean	985	1761	354	0.027
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Other physical therapies				
Mean	573	1014	215	0.013
Median (Q1–Q3)	0 (0–0)	0 (0–49)	0 (0–0)	
Physiotherapy				
Mean	187	311	86	<0.001
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Transport for medical needs				
Mean	65	112	27	<0.001
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Other costs				
Mean	6643	9799	4080	0.020
Median (Q1–Q3)	0 (0–2853)	354 (0–5632)	0 (0–1439)	
Mean annual cost per age group per patient-year, €				
0–1 year				
No. of patients, *n*	113	49	99	
Patient-years	210	61	149	
Cost (SD), €	24,434 (82,453)	53,073 (138,514)	12,709 (36,686)	<0.001
2–9 years				
No. of patients, n	204	166	167	
Patient-years	1038	496	542	
Cost (SD), €	22,996 (63,199)	31,614 (73,093)	15,110 (51,356)	<0.001
10–19 years				
No. of patients, *n*	59	38	34	
Patient-years	131	61	70	
Cost (SD), €	18,487 (45,263)	33,030 (61,799)	5813 (13,748)	<0.001

AED, antiepileptic drug; LGS, Lennox-Gastaut syndrome; Q1–Q3, interquartile range; SD, standard deviation.
[a] Rescue medication use is defined by having ≥1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate.
[b] *t*-test for patients with versus without rescue medication prescription.

3.3. Hospitalization rates and LOS

All hospitalization and LOS analyses were conducted using the narrowly defined probable LGS population ($n = 208$; 1379 patient-years).

3.3.1. All patients

During the 10-year study period, patients were admitted to hospital a mean (SD; median) of 1.6 (2.0; 1) times annually and reported a mean (SD; median) annual LOS of 22.7 (46.0; 3) days per patient-year (Table 3). The range was wide for these data;

Table 3
Summary of hospitalization rates and LOS, including stratification into patient groups with/without prescription of rescue medication[a] for patients with narrowly defined probable LGS during the 10-year study period.

	All patients		Years where patients prescribed with rescue medication[a]		Years where patients not prescribed with rescue medication[a]		*p*-value[b]	
No. of patients, *n* (%)	208 (100)		178 (86)		188 (90)			
	AHR	LOS (days)	AHR	LOS (days)	AHR	LOS (days)	AHR	LOS (days)
All patients								
Patient-years	1379	1379	618	618	761	761		
Mean (SD)	1.6 (2.0)	22.7 (46.0)	2.2 (2.3)	30.1 (55.4)	1.1 (1.6)	16.7 (35.6)	<0.001	<0.001
Median (range)	1 (0–13)	3 (0–804)	2 (0–13)	10 (0–804)	1 (0–13)	1 (0–309)		
95% CI	1.5–1.7	20.3–25.1	2.0–2.4	25.7–34.5	1.0–1.2	14.2–19.2		
All patients (due to primary probable LGS diagnosis)								
Patient-years	1379	1379	618	618	761	761		
Mean (SD)	0.7 (1.3)	10.3 (26.9)	1.1 (1.6)	15.4 (32.3)	0.4 (1.0)	6.2 (20.8)	<0.001	<0.001
Median (range)	0 (0–10)	0 (0–294)	1 (0–10)	0 (0–294)	0 (0–10)	0 (0–208)		
95% CI	0.7–0.8	8.9–11.8	1.0–1.3	12.9–18.0	0.3–0.5	4.7–7.7		
Patients hospitalized with mechanical ventilation								
Patient-years	32	32	17	17	15	15		
Mean (SD)	1.3 (0.6)	40.5 (44.6)	1.5 (0.8)	21.5 (17.3)	1.0 (0.0)	61.9 (56.0)	0.015	0.016
Median (range)	1 (1–3)	27.5 (3–181)	1 (1–3)	20 (3–66)	1 (1–1)	40 (11–181)		
95% CI	1.1–1.5	25.0–55.9	1.2–1.9	13.3–29.7	1.0–1.0	33.6–90.3		

AHR, annual hospitalization rate; CI, confidence interval; LGS, Lennox-Gastaut syndrome; LOS, length of stay; SD, standard deviation.
[a] Rescue medication use is defined by having ≥1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate.
[b] *t*-test for patients with versus without rescue medication prescription.

hospitalizations ranged from 0 to 13 and LOS from 0 to 804 days per patient-year. The main reason for hospitalization was epilepsy and recurrent seizures (G40 ICD-10 code), occurring in 87% of patients during the study; pneumonia (J18, 23%) and acute bronchitis (J20, 19%) were the next most common reasons. Patients hospitalized with mechanical ventilation had a mean (SD; median) LOS of 40.5 (44.6; 27.5) days, almost double that of the overall population.

3.3.2. Patients with prescribed rescue medication

The mean (SD) annual hospitalization rate was significantly greater in those who were prescribed with rescue medication ($n = 178$; 618 patient-years) versus those who were not ($n = 188$; 761 patient-years) (2.2 [2.3] vs. 1.1 [1.6] per patient-year, $p < 0.001$; Table 3). This trend was also observed with LOS, with a significantly longer LOS recorded in those who were prescribed rescue medication versus those who were not. Among patients who received mechanical ventilation, those prescribed with rescue medication had a much shorter mean (SD) LOS than those who were not (21.5 [17.3] vs. 61.9 [56.0] days).

3.4. Medication use

All analyses of medication use were conducted using the narrowly defined probable LGS population ($n = 208$; 1379 patient-years). During the 10-year study period, the mean (SD; median) number of different medications prescribed was 11.3 (7.3; 10) per patient-year and 33.8 (17.0; 29.5) over the entire observable time for each patient. In this same population, AEDs alone accounted for a mean (SD; median) of 2.1 (1.1; 2) of the medications prescribed per patient-year and 3.8 (2.0; 3) over the entire observable time. Patients typically received between one and three different AED combinations in each year (range: 1–9) and most patients received either two, three, or four different AEDs (29%, 24%, and 16%) [range: 1–12] over the entire observable time. During the last year of observation for each patient, the top six prescribed AEDs/AED combinations (number of patients, %) were valproate (62, 37%), lamotrigine (25, 15%), lamotrigine and valproate (16, 10%), oxcarbazepine (15, 9%), oxcarbazepine and valproate (8, 5%), and clobazam (8, 5%). Over the entire study period, the top five prescribed medications (number of patient-years, %) were ibuprofen (782, 57%), xylometazoline (744, 54%), paracetamol (609, 44%), diazepam (582, 42%), and valproate (571, 41%). Three AEDs (valproate, levetiracetam, and lamotrigine) featured within the top 20 most commonly prescribed medications.

3.5. Comorbidities

Comorbidities were common in the narrowly defined probable LGS population; comorbidity and aggregated comorbidity data are shown in Fig. 2A and B.

3.6. Injuries

During the 10-year study period, the frequency of reported injuries was concordant between the narrowly defined probable LGS population and the control group. At least one injury was reported by 67% of patients (control: 69%); injuries to the trunk (46%; vs. control: 50%) and head (41%; vs. control: 36%) were the most common injuries observed. 'Epilepsy and recurrent seizures' (G40) was the most commonly reported secondary diagnosis in all patients hospitalized due to a fracture (probable fall) during the study.

3.7. Mortality

Over the 10-year study period, the mortality rate in patients with narrowly defined probable LGS was higher than that observed in the control population (2.88% [six events] vs. 0.01% [one event], $p < 0.001$; Fig. 3A). The mortality rate was greater in the broadly defined probable LGS population versus the narrowly defined population (10.01% [157 events] vs. 2.88% [six events], $p < 0.001$; Fig. 3B).

In the narrowly defined probable LGS population, the mortality rate was 3.39% (four events) in those prescribed with rescue medication versus 2.22% (two events) in those with no prescribed rescue medication (Fig. 3C).

4. Discussion

This retrospective study provides healthcare cost and utilization data in patients with LGS in Germany. This is the first study to

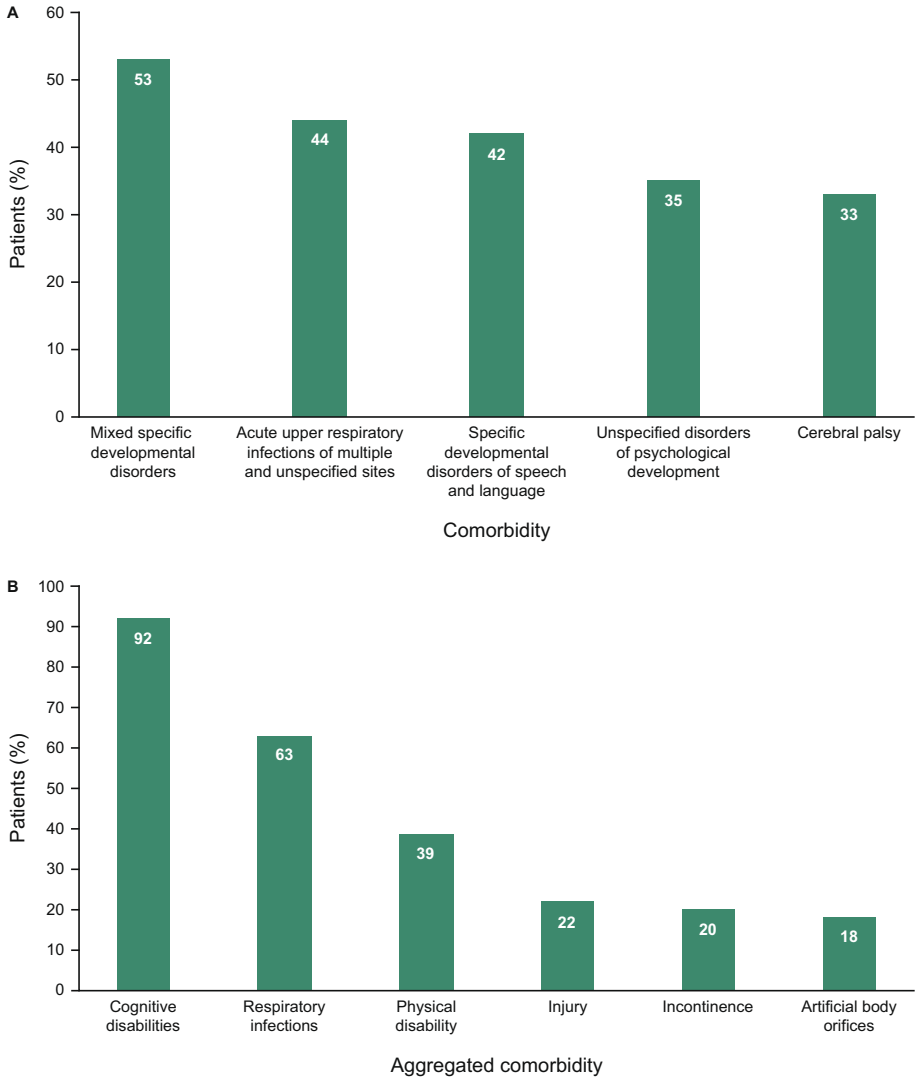

Fig. 2. Comorbidity (A) and aggregated comorbidity (B) data for patients with narrowly defined probable LGS during the 10-year study period. LGS, Lennox-Gastaut syndrome.

report direct cost analyses for patients with LGS within Europe. Furthermore, few studies have reported the prevalence of LGS, with some published over 20 years ago [22,23]. The present study adds important recent epidemiological data to a small field and provides a foundation for further research. These data from the Vilua Healthcare research database cover a 10-year period up to 2016 and are representative of the German population covering 5% of the total population. Within this, the study provides a good representation of the two probable LGS patient groups (broadly defined and narrowly defined probable LGS).

In the final year of our study (2016), the selection algorithm identified 545 patients with probable LGS (broadly defined); an additional criterion was applied (≥1 epilepsy diagnosis <6 years of age) to increase the specificity of the patient selection algorithm and strengthen the likelihood of selecting patients with LGS. The application of this further stratification selected 102 patients from the previous 545 (narrowly defined probable LGS). It should be noted that patients were not excluded because they definitely did not have LGS, but rather because there was less certainty around their diagnosis as the age criterion with onset <6 years of age could only be applied to a subset of patients (those born after January 1, 2001). The lack of a specific code for LGS is a limitation of all retrospective analyses that use healthcare database data. The introduction of ICD-11 in the healthcare community will in future yield data from which patients with LGS will be easier to identify, providing that recommended data entry protocols are followed and an ICD code for LGS is adopted.

In 2016, for the broadly and narrowly defined probable LGS populations, the standardized prevalence was 39.2 and 6.5 per 100,000 people. A previous study of children in the USA aged 10 and born between 1985 and 1987 noted a prevalence rate of 26 per 100,000 for probable LGS [23]. The inclusion criteria used in the previous study classified all patients with mixed types of generalized seizures and intellectual disability as having probable LGS [23]. In comparison, the present study employed selection criteria that were based on previous analyses [6,11,13], but attempted to increase algorithm accuracy by stratifying patients with probable LGS based on age at diagnosis.

Our findings agree with previously published analyses that the healthcare costs associated with LGS are significant [6,11,13]. All previous studies note that the mean annual costs associated with probable LGS are very high; where the comparison has been shown, these costs exceed those of patients without LGS (Appendix Table S2), and also exceed those of other encephalopathies such as DS and TSC [14]. In the present study, the largest component of direct healthcare costs was inpatient care (33%). This trend is

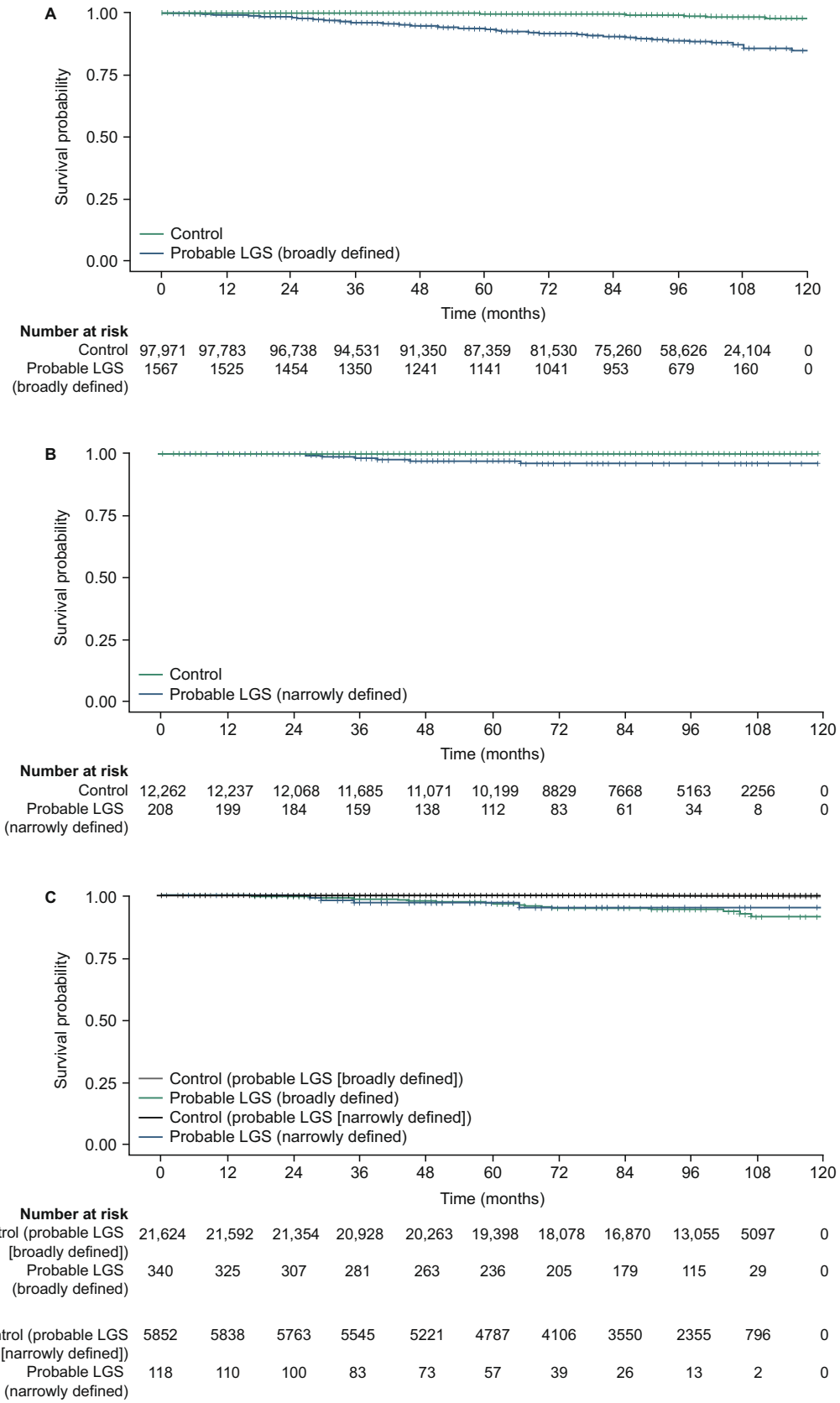

Fig. 3. Survival rate of patients with probable LGS and the control group[a] during the 10-year study period (A – broadly defined; B – narrowly defined; C – probable LGS with ≥1 recorded instance of rescue medication prescription[b] during the study period [broadly and narrowly defined]). LGS, Lennox-Gastaut syndrome. [a] The control group consists of individuals of the same age and sex distribution over an equal observation time. [b] 'Rescue medication prescription' is defined by having at least one prescription of midazolam, diazepam (rectal formulation), or chloral hydrate.

reflected by previous analyses of probable LGS, which showed that hospitalization and inpatient-related expenses represented the bulk of mean annual costs. It should be noted that the current study only presents data from the child and adolescent population (maximum age included: 14 years) due to the stratification algorithm employed; direct comparisons with other studies in patients with probable LGS with wider age ranges are therefore limited. The substantial cost of home nursing care (13% of total costs) is also noteworthy and highlights that children with LGS have complex medical and physical needs and often require continuous care.

In the present study, the rate of hospital admissions was considerable (mean: 1.6 per patient-year) and annual LOS was long (mean: 22.7 days) for those within the narrowly defined probable LGS population. Most hospitalizations were the result of epilepsy and/or recurrent seizures, indicating that there is still a high unmet treatment need in this population. It should be noted that there was at least one instance of very long hospitalization (>804 days). This trend was reflected in annual cost data: there was again at least one instance of very high inpatient-related costs (range: €0–€524,838).

Our findings are broadly consistent with previous studies that have observed frequent inpatient admissions among populations with LGS and other epilepsies. Two studies conducted in the USA reported lower hospitalization rates for patients with probable LGS (0.3–0.7 per patient-year), although direct comparisons between studies are limited by methodological differences [11,13]. In line with our analysis, one of these studies reported that seizure-related inpatient visits represented roughly two-thirds of all inpatient visits for patients with probable LGS [13]. A survey conducted in Germany found that 15.7% of children and adolescents with epilepsy were admitted to hospital at least once over a 3-month period with a mean LOS of 9.3 days [12]. It is interesting to note that our findings regarding high hospitalizations in patients with probable LGS are also in line with those reported in two similar recent bottom-up analyses of healthcare data from patients with DS, another epileptic encephalopathy [24,25]. In particular, both studies observed considerable inpatient LOS in patients with DS. In the first study, mean LOS due to DS was 25.6 days over the previous 12 months [24]. The second study compared patients with DS to age- and sex-matched patients either with drug-resistant epilepsy (without encephalopathy) or in seizure remission. LOS in the DS group was comparable with that in patients with drug-resistant epilepsy (2.5 and 2.9 days over 3 months) and significantly longer than for those in seizure remission (0.3 days over 3 months) [25].

Patients with prescribed rescue medication incurred costs significantly greater than those of patients without (€33,872 vs. €13,785 per patient-year, $p < 0.001$). Those patients with prescribed rescue medication also had a significantly higher annual hospitalization rate and longer LOS. Interestingly, mortality was similar between those prescribed with rescue medication and those who were not (3.39% vs. 2.22%). Several clinical or social factors may have influenced costs and hospitalizations in patients who were prescribed rescue medication, but it is beyond the scope of this analysis to evaluate such factors. It should be noted that all comparisons of those prescribed versus not prescribed rescue medication are limited by the difference in size of these populations; few patients did not receive rescue medication at least once during the study.

As expected in this population, patients were prescribed multiple medications including AEDs. However, the number of different AEDs prescribed for each patient was generally low, suggesting that AED treatment remained relatively stable throughout the study period. This is supported by the fact that most patients received either two, three, or four different AEDs (29%, 24%, and 16%) over the entire observable time. The most commonly prescribed AEDs in this study were valproate and lamotrigine; this is in keeping with current expert opinion for the treatment of LGS [4]. This trend was also observed in previous studies of patients with probable LGS: patients generally used more non-AED versus AED medications, and the number of different AEDs prescribed was low [11,13]. The present study also shows that a few patients were prescribed very expensive non-AED medications which influenced mean treatment costs.

Over two-thirds of the narrowly defined probable LGS population reported at least one injury. This may be partly explained by the high incidence of drop seizures in patients with LGS. Drop seizures tend to occur suddenly and with the potential to cause significant injury [3]. Interestingly, however, there was no marked difference between the frequency of injuries in patients with narrowly defined probable LGS and matched controls. Each probable LGS patient was matched to at least 100 Vilua Healthcare database entries of the same age, sex, and observation time. Consequently, the matched control population would be aged ≤15 years and it is likely that a large proportion of this pediatric population would have experienced at least one injury across a 10-year period.

In line with other published data in patients with LGS, most patients in this study had other comorbidities besides epilepsy [1,26,27], emphasizing the need for the impact of this additional burden to be considered when contemplating both the costs associated with LGS and the treatment plans that should be offered in its management. In the present study, the most common aggregated comorbidities were cognitive disabilities, although this is unsurprising as cognitive disabilities formed part of the possible patient selection criteria. The next most common comorbidities were respiratory infections, physical disabilities, and injuries. It is unclear if these comorbidities influenced the costs reported in this study and this could form the basis for future analyses.

This study reports a mortality rate of 2.88% for patients with narrowly defined probable LGS, which is comparable with other published data for patients with LGS, which report mortality as between 3% and 7% [26–28]. Six patients aged ≤14 years died over the 120 months of the present study. Since death in LGS can often be attributed to status epilepticus, the result of an accident during a seizure or sudden unexpected death in epilepsy [29–31], these findings underline the unmet need in LGS as improved seizure control may reduce mortality [2].

5. Limitations

Although our selection algorithm was informed by the methodology of previous studies in LGS and other encephalopathies [6,11,13], it is possible that misclassification of LGS patients may have occurred. In addition, the analyses were based on healthcare insurance data; there may have been inaccuracies such as under- or over-reporting within the Vilua Healthcare research database. Although the requirement for ≥1 epilepsy diagnosis <6 years of age for inclusion in the narrowly defined population may have increased the sensitivity of the study, this excluded older patients with LGS from the study population. This was unavoidable due to the study duration (2007–2016) and the retrospective nature of the analysis i.e. the need to verify a diagnosis before age 6 within the 10-year study period. A prospective study that enrolls patients following diagnosis would remove this exclusion, although data would take many years to acquire. The present study was 10 years in length and enrolled patients at different ages; individual patients within the study may not have been longitudinally present across all of the age categories they were captured within at study conclusion. Patients with prescribed rescue medication were identified in our analysis as those who were prescribed midazolam, diazepam (rectal formulation), or chloral hydrate. However, recent

data have indicated that unsuitable benzodiazepines with slow absorption rate or off-label products are frequently used as emergency medication for adults with epilepsy in Germany [20]. Thus, our definition may have been too narrow to identify all prescriptions that were intended for use as rescue medication. Also, patient data reviewed within this study were exclusively obtained from the German Vilua Healthcare database. The hospitalization rate may be high in Germany compared with other countries, with 12% of the general population reporting inpatient treatment over 6 months [32]. Hospitalizations in patients with active epilepsy, however, have remained stable in Germany over the past decade [33]. Further research is necessary to validate the outcomes of this study and ensure that findings are applicable to patients with LGS across Europe and the rest of the world.

6. Conclusions

This study presents a German healthcare database analysis that provides a welcome assessment of the epidemiology and characteristics of LGS within Europe. Annual healthcare costs incurred by those with probable LGS were substantial; inpatient care, home nursing care, and medication were the greatest contributors to these costs. Patients prescribed with rescue medication incurred significantly greater costs than those who were not. Patients with probable LGS with epilepsy diagnosis before 6 years of age had a higher mortality rate versus control populations.

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All authors met the International Committee of Medical Journal Editors authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship.

Author contributions

All authors contributed to the study concept, design, and interpretation of the data. ASi analyzed the data.

Data-sharing statement

The sponsor adheres to current requirements of the USA and the European Union and so will not make individual de-identified participant data available; however, the protocol and statistical analysis plan will be made available upon request to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107647.

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