

Epidemiology and Burden of Illness of Lennox-Gastaut Syndrome in Taiwan: A Retrospective Cohort Study

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Purpose: Examine the epidemiology and burden of illness of patients with Lennox-Gastaut syndrome (LGS) in Taiwan.

Methods: The National Health Insurance Database (NHID) was used, complemented by the Chang Gung Research Database (CGRD). Confirmed LGS was defined by International Classification of Diseases-10 (ICD-10) LGS codes or ≥ 1 rufinamide prescription; probable LGS was defined as patients aged ≤ 10 years when receiving ≥ 3 antiseizure medications (ASMs), with ICD-9/10 codes for developmental delay. Independent clinical review/validation of all LGS cases in the CGRD was conducted. Prevalence, incidence, time to treatment/LGS diagnosis, hospitalizations, costs (US dollars), ASM usage, and mortality were assessed. For the NHID, a positive predicted value (PPV) was calculated from the CGRD validation step to adjust prevalence/incidence estimates.

Results: In the NHID, 190 patients with confirmed LGS were identified. In 2018, PPV-adjusted prevalence was 2.4, 0.6, and 10.2 per 100,000 people and PPV-adjusted incidence was 0.6, 0.2, and 2.4 per 100,000 person-years in the total, adult, and pediatric populations, respectively. Of 92 (48%) hospitalized patients, 22 (24%) had ≥ 3 hospitalizations/year. Mean (standard deviation [SD]) time to treatment and LGS diagnosis were 12.3 (26.5) and 110.1 (54.7) months. Mean length of stay was around 12 days. Most hospitalizations (96%) were epilepsy related. Mean (SD) hospitalization cost was \$237 (\$216) per day. Mean (SD) total inpatient and outpatient costs were \$5800 (\$817) and \$2667 (\$132), respectively, per patient per year (PPPY); medication in hospital and ASM costs were \$1910 (\$108) and \$1614 (\$93) PPPY. Most prescribed ASMs were valproate (89%), levetiracetam (83%), clonazepam (69%), clobazam (68%), and topiramate (65%). Mortality was 0.01 deaths per 100,000 people in 2018.

Conclusion: Although prevalence and incidence of LGS in Taiwan were lower than in other countries, the multifaceted burden of illness in LGS is highlighted herein. Reduced hospitalizations through better epilepsy control may reduce LGS expenditure.

Keywords: epilepsy, healthcare resource utilization, incidence, LGS, prevalence

Introduction

Lennox-Gastaut syndrome (LGS) is a rare, severe, developmental epileptic encephalopathy primarily with childhood onset, typically diagnosed in children younger than 8 years with a peak age at onset of 3–5 years, and is associated with high mortality rates^{1,2} (up to 35%; 14 times higher than the general population in the USA).^{3,4} Global LGS prevalence varies from 2.9 to 28.0 per 100,000 people, and incidence has been previously reported at 16.0 per 100,000 person-years, around 1.9 per 100,000 people, and 14.5–28.0 per 100,000 live births.^{2,3} LGS is characterized by treatment-resistant

seizures of multiple types, typically with onset before 18 years of age, cognitive and behavioral impairments, and diffuse slow spike-and-wave and generalized paroxysmal fast activity on electroencephalogram (EEG).¹ Management and treatment of LGS are challenging owing to treatment-resistant seizures, polypharmacy, and associated co-occurring symptoms.⁵ This results in considerable healthcare resource utilization (HCRU) and costs, and a high burden of illness.^{2,6–9} Improved understanding of the worldwide epidemiology and burden of illness of LGS is needed to determine the disease impact on healthcare systems and society.

Previous studies published in 2012 and 2018 have reported the prevalence of rare diseases and epilepsy in Taiwan.^{10,11} However, there is a scarcity of recent evidence of the epidemiologic and economic impact of LGS in Taiwan. This retrospective cohort study investigated for the first time the epidemiology and burden of illness of patients diagnosed with LGS in Taiwan using the National Health Insurance Database (NHID). Additionally, validated LGS cases from the Chang Gung Research Database (CGRD) were examined to strengthen the NHID findings.

Materials and Methods

Data Sources

NHID

The NHID is a nationwide claims database containing medical records from around 23 million individuals in Taiwan, accounting for $\geq 99.9\%$ of the population in 2014.^{12,13} The database provides extensive records, including diagnoses, drug prescriptions and dispensations, procedures, and HCRU across various settings,¹⁴ all linked via an encrypted unique patient-level identifier to other databases including the National Death Registry. Detailed information regarding the nature of the NHID data has been previously published.¹² The NHID has been used previously for epidemiological studies of epilepsy;^{10,15,16} however, this study is the first time it has been used to investigate LGS epidemiology.

CGRD

The CGRD is derived from 7 Chang Gung Memorial hospitals (CGMHs),¹³ covering around 1.2 million patients in Taiwan (6% of outpatients; 10% of inpatients) and accounting for $\sim 5\%$ of Taiwan's population in 2020 (N=23,561,236).¹⁷ The CGRD is an electronic medical record (EMR)-based database containing test results and physician notes on diagnoses not captured in claims databases,¹³ and has been used in several previous studies.^{18–20}

Patient Identification and Inclusion Period

An identification algorithm was developed to identify patients with LGS from records extracted over a 12-year assessment period from the NHID (January 1, 2007 to December 31, 2018) and a 10-year period from the CGRD (January 1, 2011 to December 31, 2020). Differences in the assessment periods between databases were due to inherent lag times for data acquisition. Health conditions were coded with International Classification of Diseases Ninth Revision (ICD-9 [before 2016]) or Tenth Revision (ICD-10 [2016 onwards]) codes in both databases.^{13,21} The patient identification algorithm of both databases identified patients with the presence of 2 or more records of epilepsy diagnosis using ICD-10 codes for epilepsy, status epilepticus (ICD-10: G40/G41) or ICD-9 code 345 for epilepsy ([Figure 1](#) and [Supplementary Figure 1](#)). The cohort was then evaluated to identify cases of confirmed or probable LGS. Confirmed LGS was defined by ICD-10 LGS codes (all G40.81 codes) or at least one rufinamide prescription. Rufinamide was used as a surrogate for LGS diagnosis based on its exclusive label and reimbursement criteria in Taiwan (rufinamide's approval in 2017; reimbursement for LGS after 2017). An algorithm to identify probable LGS was used to account for potential underdiagnosis (ie identifying patients with clinical characteristics, but no recorded diagnosis of LGS). Probable LGS was defined as patients aged 10 years or younger when simultaneously prescribed 3 or more antiseizure medications (ASMs), with any ICD-9/10 code for developmental delay ([Supplementary Table 1](#)), and with no diagnostic codes for other etiologies ([Supplementary Table 2](#)).

To determine the accuracy of the confirmed and probable LGS identification algorithms, a manual chart review and a pre-specified clinical validation algorithm were conducted in the CGRD ([Supplementary Figure 1](#)). Each chart was independently reviewed, based on genetic tests, clinical diagnosis, and/or symptoms and EEG patterns in the EMR, and validated by 2 expert clinicians (authors: CCW, WMC). If consensus was not achieved, clinicians would discuss patients'

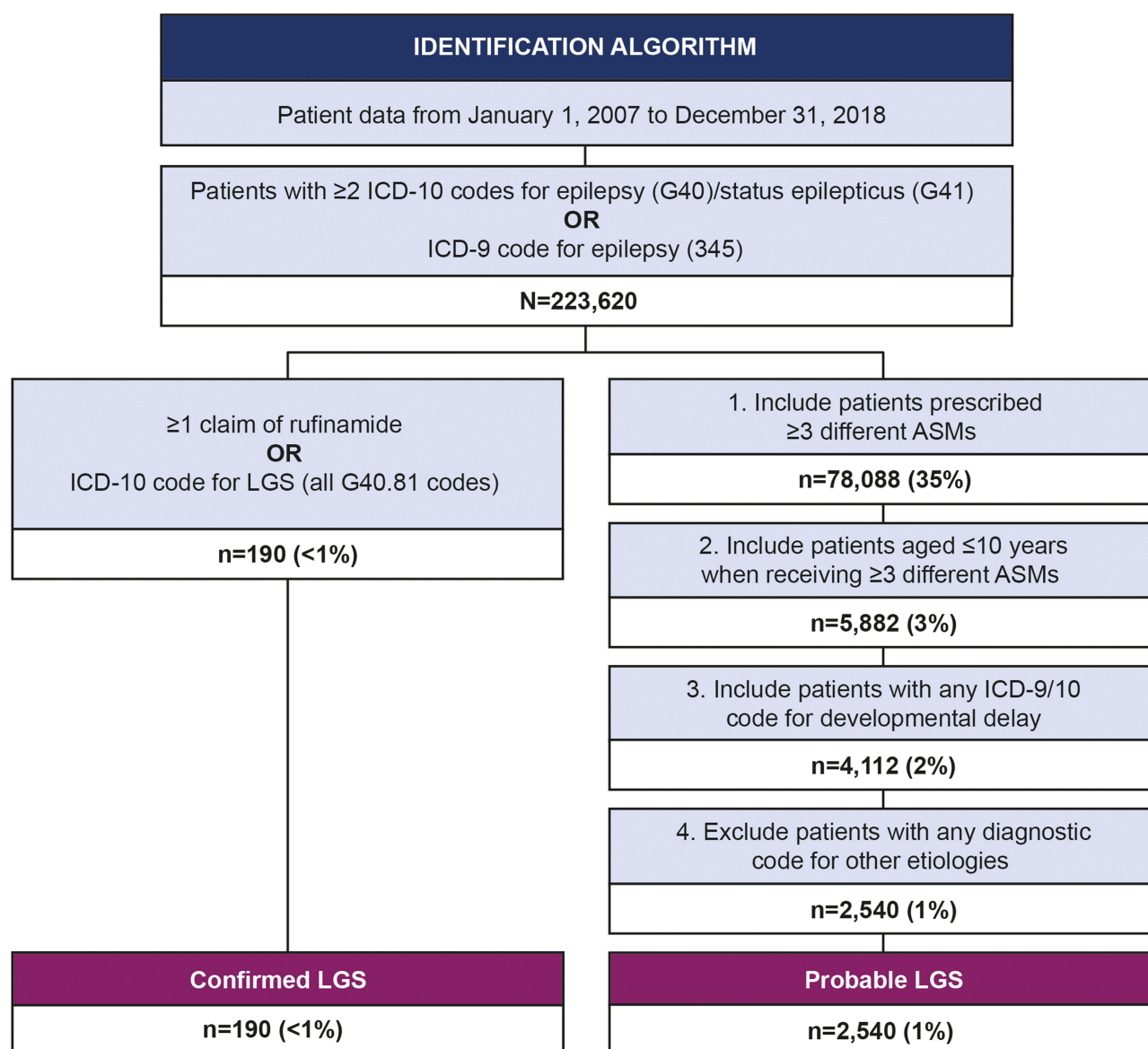


Figure 1 Patient Identification Algorithm (NHID).

Abbreviations: ASM, antiseizure medication; ICD-9/10, International Classification of Diseases Ninth/Tenth Revision; LGS, Lennox-Gastaut syndrome; NHID, National Health Insurance Database.

records with a senior pediatric neurologist (author: LWC). Cases were classified as “validated LGS” if the EMR contained details of a history of developmental delay or cognitive impairment (captured in the unstructured patient notes), in addition to the presence of either EEG abnormalities, or multiple seizure types.

Index date was defined for confirmed LGS as the first diagnostic date among assessment periods, or for probable LGS as the first date of simultaneous prescription of 3 or more ASMs in the whole follow-up period in patients aged 10 years or younger.

Primary outcomes were reported for confirmed and probable LGS cases from the NHID, and for validated (confirmed and probable) LGS cases from the CGRD. Secondary outcomes focused on confirmed LGS cases from the NHID. Findings from the validated (confirmed and probable) LGS cases from the CGRD are shown in the [Supplementary Material](#).

Time to diagnosis of LGS (confirmed or probable) was defined as the time between the first diagnosis of epilepsy and index date. Time to treatment was defined as time from the first diagnosis of epilepsy to first ASM prescription. Time to

injury or intellectual disability (ID) was defined as the time between index date and first event. Details of co-occurring symptoms ([Supplementary Tables 1 and 2](#)), ASMs ([Supplementary Table 3](#)), injuries ([Supplementary Table 4](#)), and ID ([Supplementary Table 5](#)) are reported in the [Supplementary Material](#).

Outcomes

Primary outcomes were the epidemiology profiles of LGS (prevalence and incidence). As LGS cases from the NHID used the identification algorithm only (ie not clinician validated), a positive predictive value (PPV) based on the clinically validated LGS cases from the CGRD was applied to the prevalence and incidence estimates (“PPV-adjusted prevalence/incidence”) of the NHID to improve accuracy – assuming the same estimation error in the CGRD and NHID. The PPV describes the precision of the LGS identification algorithm, indicating the probability that an identified case that is a true case, with a PPV of 100% indicating a perfectly accurate algorithm.

Prevalence and incidence for the NHID used denominators from the National Development Council.¹⁷ To align with the denominator data, pediatric and adult populations were defined as patients aged 0–18 years and >18 years, respectively. For the CGRD, a denominator of 10% of Taiwan’s annual population was used; this denominator was chosen considering the CGRD enrolls around 10% of hospitalized patients from the NHID.¹³

Secondary outcomes included time from first epilepsy diagnosis to first ASM prescription and to LGS diagnosis, HCRU (hospitalizations for all causes/epilepsy [identified by ICD-9/10 coding], hospitalization rates, length of stay [LOS]), healthcare costs (hospitalizations, medications, total healthcare), ASM usage from 16 protocol-prespecified ASMs (based on Anatomical Therapeutic Chemical [ATC] codes, [Supplementary Table 3](#)), injuries (based on ICD codes, [Supplementary Table 4](#)), ID (based on ICD codes, [Supplementary Table 5](#)), and mortality. Mortality rates were calculated from the number of deaths divided by Taiwan’s annual total population for the NHID, or by 10% of Taiwan’s annual total population for the CGRD. Patients were followed from the index date until death or loss to follow up (applicable in CGRD, defined as no medical visit record for more than 1 year) or end of study period, whichever came first.

Primary outcomes were reported either yearly or aggregated from 2016 until the end of each database assessment period. Patient demographics and secondary outcomes were reported based on the years with available confirmed LGS cases (NHID: since 2016; CGRD: since 2011). ASM usage was reported for the entire study period, and outcomes for patients with injuries or ID were reported after the index date. For injuries and ID outcomes, patients with corresponding outcomes prior to the index date were excluded based on a one-year look back ([Supplementary Figure 2](#)) to better measure incident event rates.

Economic Analyses

Healthcare information (inpatients and outpatients) is included in the calculations for total healthcare costs.^{12,13} All costs are shown in US dollars (\$) following conversion from New Taiwan dollars (NTDs) using a ratio of 30:1 (NTD:\$) based on the mean exchange rate from the National Bank of Taiwan in 2018.

Statistical Analyses

Descriptive data are presented for continuous variables by means and standard deviation (SD), and categorical variables by number with proportion. The PPV was calculated from the number of validated cases (true positives)/total number of identified cases (true positives + false positives) in the CGRD. In a pre-specified subgroup analysis, inpatient and outpatient costs were compared between patients with/without injury or ID using a two-tailed Student’s *t*-test. Data were analyzed using SAS® version 9.4.0 software (North Carolina, USA).

Results

Patient Demographics and Baseline Characteristics

In the NHID, a total of 190 patients with confirmed LGS and 2540 patients with probable LGS were identified ([Figure 1](#)). Among confirmed cases, 92 (48%) patients were identified based on the prescription of rufinamide, and 98 (52%) patients based on ICD-10 coding. In the CGRD, 95 patients with confirmed LGS and 291 patients with probable LGS were

identified ([Supplementary Figure 1](#)); following chart review, 187 cases were validated, resulting in a PPV of 68% for confirmed (n=65/95) and 42% for probable LGS (n=122/291).

For confirmed LGS in the NHID, mean (SD) age at index date was 18.9 (12.1) years. Most patients were male (120 [63%]) with developmental delay (155 [82%]) and/or abnormal brain development (91 [48%]). Characteristics for patients with probable LGS in the NHID are shown in [Table 1](#). Patients with validated LGS in the CGRD had a mean (SD) age at index date of 10.2 (9.3) years, were mostly males (116 [62%]), and most had developmental delay (162 [87%]) and/or abnormal brain development (79 [42%]) ([Table 1](#)). Although epilepsy surgery is not reimbursed under the NHID, resulting in a lack of corresponding data, 14 patients in the CGRD underwent epilepsy surgery, and 12 received vagus nerve stimulation.

Prevalence and Incidence

The prevalence of LGS numerically increased from beginning to end of the study periods in both databases. [Table 2](#) shows the prevalence and incidence of LGS over the study period in the total, adult, and pediatric populations, and by sex in both databases. In the NHID, 148 patients (73 [49%] children) with confirmed LGS and 1092 patients (949 [87%] children) with probable LGS were identified in 2018, the most recent year evaluated. The PPV-adjusted prevalence per 100,000 people for this year was 2.4, 0.6, and 10.2 in the total, adult, and pediatric populations, respectively. In the CGRD, a total of 164 patients (121 [74%] children) with validated LGS were identified in 2020 (the most recent year evaluated), resulting in a prevalence per 100,000 people of 6.7, 2.2, and 29.4 in the total, adult, and pediatric populations, respectively. Prevalence in the total male cohort was numerically higher than in females.

In the NHID, based on 83 patients (43 [52%] children) with confirmed and 192 patients (185 [96%] children) with probable LGS identified in 2018, PPV-adjusted incidence of LGS per 100,000 person-years was 0.6, 0.2, and 2.4 for the total, adult, and pediatric populations, respectively. In the CGRD, based on 19 patients (15 [79%] children) identified in

Table 1 Patient Baseline Characteristics for Both Databases

	NHID Confirmed LGS	NHID Probable LGS	CGRD Validated LGS
	N=190	N=2540	N=187
Age (years) at index date,^a mean (SD)	18.9 (12)	4.0 (3)	10.2 (9)
Age (years) at index date^a by age category, n (%)			
0–3	16 (8)	1295 (51)	51 (27)
4–5	9 (5)	379 (15)	18 (10)
6–12	35 (18)	866 (34)	68 (36)
13–17	37 (20)	0	13 (7)
≥18	93 (49)	0	37 (20)
Time (months) to treatment, mean (SD)	12.3 (27)	4.0 (20)	0.1 (1)
Time (months) to diagnosis, mean (SD)	110.1 (55)	15.1 (23)	44.1 (39)
Sex, n (%)			
Female	70 (37)	1101 (43)	71 (38)
Male	120 (63)	1439 (57)	116 (62)
Co-occurring symptoms, n (%)			
Developmental delay ^b	155 (82)	2540 (100)	162 (87)
Other etiologies ^c	73 (38)	0 (0)	34 (18)
Abnormal brain development	91 (48)	1111 (44)	79 (42)

Notes: Data reported for patients with an index date within 2016–2018 (NHID, confirmed LGS), 2007–2018 (NHID, probable LGS), and within 2011–2020 (CGRD). ^aIndex date was determined based on either the date of first diagnosis (confirmed LGS) or the date of first simultaneous prescription of ≥3 ASMs (probable LGS); for probable LGS, the age of diagnosis was ≤10 years. ^bIdentified using ICD-9/10 diagnosis codes for developmental delay ([Supplementary Table 1](#)). ^cData on other developmental etiologies apply to confirmed LGS only. ICD-9/10 diagnosis codes for other etiologies can be found in [Supplementary Table 2](#).

Abbreviations: ASM, antiseizure medication; CGRD, Chang Gung Research Database; ICD-9/10, International Classification of Diseases Ninth/Tenth Revision; LGS, Lennox-Gastaut syndrome; NHID, National Health Insurance Database; SD, standard deviation.

Table 2 Prevalence and Incidence of LGS for Both Databases

Index Date	NHID Confirmed and Probable LGS				CGRD Validated LGS					
	2016	2017	2018	2016–2018	2016	2017	2018	2019	2020	2016–2020
PPV-adjusted prevalence (for NHID)/prevalence (for CGRD) (per 100,000 people)										
Total population	2.0	2.2	2.4	2.2	3.3	3.7	4.8	6.3	6.7	4.8
Males	2.5	2.6	2.8	2.6	4.0	4.9	6.2	8.0	8.8	6.1
Females	1.6	1.8	1.9	1.8	2.5	2.6	3.5	4.6	5.1	3.5
Adult population (aged >18 years)	0.2	0.3	0.6	0.4	NA	0.3	1.2	1.7	2.2	NA ^a
Pediatric population (aged 0–18 years)	9.4	10.3	10.2	9.9	16.8	18.7	20.6	27.0	29.4	22.0
PPV-adjusted incidence (for NHID)/incidence (for CGRD) (per 100,000 person-years)										
Total population	0.6	0.6	0.6	0.6	0.4	0.6	1.3	1.7	0.8	0.8
Males	0.7	0.6	0.7	0.7	0.3	0.6	0.6	1.6	0.7	0.7
Females	0.5	0.6	0.4	0.5	0.4	0.6	2.0	1.8	0.9	1.0
Adult population (aged >18 years)	0.1	0.1	0.2	0.1	NA	0.3	0.9	0.4	0.2	NA ^a
Pediatric population (aged 0–18 years)	2.7	2.9	2.4	2.7	2.0	2.0	3.0	7.5	3.6	3.2

Notes: For the NHID, the denominators were provided from the National Development Council;¹⁷ for the CGRD, a denominator of 10% of Taiwan's annual population was used. Pediatric and adult populations were defined as patients aged 0–18 years and as patients aged >18 years, respectively, to align with the denominator data. ^aDue to the lack of available data for the year 2016, prevalence/incidence data for the index period of 2016–2020 could not be calculated for the CGRD.

Abbreviations: CGRD, Chang Gung Research Database; LGS, Lennox-Gastaut syndrome; NA, not available; NHID, National Health Insurance Database; PPV, positive predictive value.

2020, incidence of validated LGS per 100,000 person-years was 0.8, 0.2, and 3.6 in the total, adult, and pediatric populations, respectively. Some numerical differences in incidence were observed between total male and female cohorts.

Time from First Epilepsy Diagnosis to ASM Treatment or LGS Diagnosis

For patients with confirmed LGS in the NHID, mean (SD) time to treatment was 12.3 (26.5) months, and time to LGS diagnosis was 110.1 (54.7) months (Table 1). In patients with validated LGS in the CGRD, mean (SD) time to treatment and time to LGS diagnosis were 0.1 (1.0) months and 44.1 (39.0) months, respectively. Values for patients with probable LGS are also shown in Table 1.

Healthcare Resource Utilization and Costs

Frequency, Length of Stay, and Cost of Hospitalization

A total of 92 (48%) patients with confirmed LGS in the NHID had 1 or more hospitalizations for any cause, with 22 (24%) patients having 3 or more per year (Table 3). Average (SD) LOS was 11.8 (15.1) days, with 48 (52%) patients staying for 7 or more days. Mean (SD) costs of hospitalization were \$237 (\$216) per day and \$2776 (\$3222) per

Table 3 Healthcare Resource Utilization and Costs After Index Date (NHID, Confirmed LGS)

	All Causes	Epilepsy
Patients with ≥1 hospitalization, n (%)	92 (48)	88 (46)
Annual hospitalization rate per patient, mean (SD)	3.0 (2.7)	2.6 (2.3)
Number of hospitalizations per year, n (%)		
<3 hospitalizations	70 (76)	69 (78)
3–5 hospitalizations	11 (12)	10 (11)
≥6 hospitalizations	11 (12)	9 (10)

(Continued)

Table 3 (Continued).

	All Causes	Epilepsy
LOS^a (days), mean (SD)	11.8 (15.1)	12.8 (25.5)
LOS, n (%)		
<24 hours	0 (0)	0 (0)
1–6 days	44 (48)	41 (47)
≥7 days	48 (52)	47 (53)
Cost of stay (\$), mean (SD)^b		
Per hospitalization day per patient	237 (216)	235 (218)
Per episode of hospitalization per patient	2776 (3222)	2637 (3742)

Notes: Data reported for patients with an index date within 2016–2018. The proportions reported are based on the total number of patients admitted to hospital. ^aDefined as the total hospital admission days after index date per total numbers of hospital admissions after index date diagnosis. ^bCosts are shown in US dollars (\$) following conversion from New Taiwan dollars (NTDs); conversion was based on a ratio of 30:1 (NTD:\$).

Abbreviations: LGS, Lennox-Gastaut syndrome; LOS, length of stay; NHID, National Health Insurance Database; SD, standard deviation.

hospitalization. Similar results were observed for epilepsy hospitalizations. HCRU and healthcare costs for patients in the CGRD are shown in [Supplementary Table 6](#).

Medication Costs

Mean (SD) costs for patients with confirmed LGS in the NHID were \$1910 (\$108) per patient per year (PPPY) for total medications in hospital (all medications prescribed during hospitalization) and \$1614 (\$93) PPPY for ASMs (includes all ASMs and rescue medications), the latter representing 85% of the total medication in hospital cost. Data for patients in the CGRD are presented in [Supplementary Table 7](#).

Total Healthcare Costs

Mean (SD) inpatient and outpatient costs for patients with confirmed LGS in the NHID were \$5800 (\$817) and \$2667 (\$132) PPPY, respectively, with similar costs observed in patients with an injury (\$4956 [\$864], and \$2675 [\$251] PPPY, respectively) or with an ID (\$6425 [\$1278], and \$2719 [\$232] PPPY, respectively) ([Supplementary Table 8](#)). Data for patients in the CGRD are presented in [Supplementary Tables 7](#) and [9](#).

ASM Usage

ASMs used in 20% or more patients with confirmed LGS in the NHID, based on the 16 protocol-prespecified ASMs, were valproate (89%), levetiracetam (83%), clonazepam (69%), clobazam (68%), topiramate (65%), perampanel (55%), zonisamide (53%), and benzodiazepines (excluding clobazam and clonazepam) (49%) ([Figure 2](#)). ASM usage data for patients in the CGRD are shown in [Supplementary Figure 3](#).

Injuries and Intellectual Disability

For patients with confirmed LGS in the NHID, there were 133 without prior injury before diagnosis of LGS ([Table 4](#)). Of these, 36 (27%) patients reported an injury after index date, with an average time from index date to first injury of approximately 14 months. A total of 135 patients were at risk of developing ID after the LGS diagnosis: 21 (16%) patients developed ID after index date, with an average time from index date to first ID of approximately 16 months ([Table 4](#)). Data are shown in [Supplementary Table 10](#) for patients in the CGRD.

Mortality

In the NHID, for patients with confirmed LGS, mortality rates were 0.01 per 100,000 people between 2016 and 2018. In the CGRD, for patients with validated LGS, mortality rates were 0.04–0.08 per 100,000 people between 2016 and 2020.

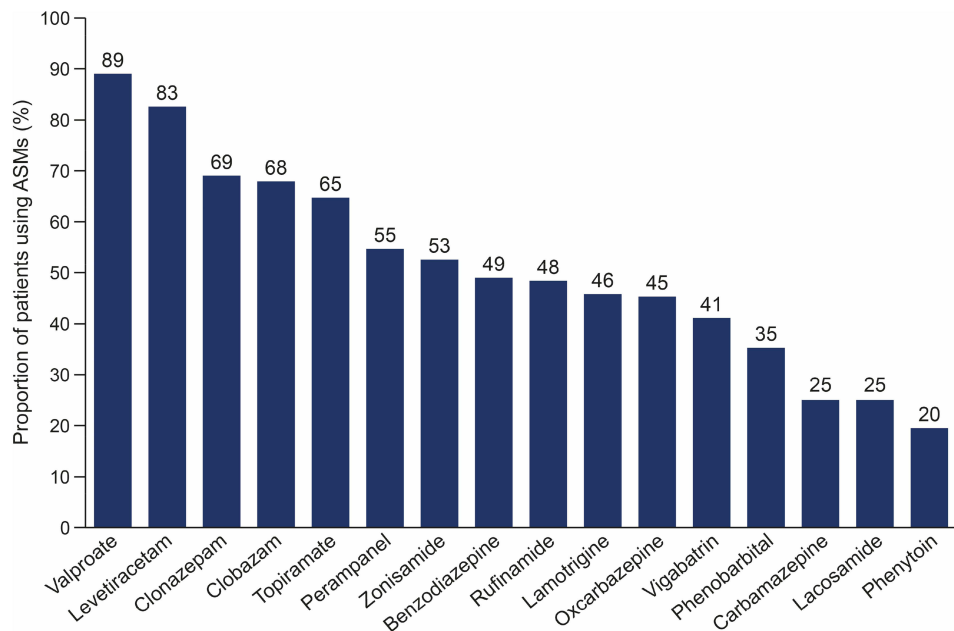


Figure 2 Treatment Patterns of ASMs (NHID, Confirmed LGS).
Notes: Data reported for patients with an index date within 2016–2018. All the protocol-prespecified ASMs (Supplementary Table 3) are shown in the figure.
Abbreviations: ASM, antiseizure medication; LGS, Lennox-Gastaut syndrome; NHID, National Health Insurance Database.

Discussion

This is the first known retrospective study evaluating the epidemiology and burden of illness of patients diagnosed with LGS in Taiwan using real-world, nationwide data. Recent epidemiological evidence using a patient identification approach demonstrated that prevalence and incidence of LGS in Taiwan were lower than reported in other countries^{2,3} and confirms its rare disease status in Taiwan. Significant HCRU and healthcare costs were associated with LGS, with inpatient and epilepsy-specific care being key drivers of costs and hospitalizations. Although the prevalence and incidence results reported herein for LGS in Taiwan are lower than previously reported in other countries, the multifaceted burden of illness in patients with LGS in the country is underscored.

In this study, 190 patients were identified with confirmed LGS from the NHID using a comparable patient identification algorithm to that used previously by claims database studies (LGS identified by ICD-9/10 codes for epilepsy, ID/developmental delays, and prescription of rufinamide), apart from the use of the specific LGS ICD-10

Table 4 Injuries and ID Reported After Index Date (NHID, Confirmed LGS)

Patients at Risk of Developing Injuries, n/N (%) ^{a–d}	133/190 (70)
Patients who developed any injury	36 (27)
Minor injury	21 (16)
Moderate injury	12 (9)
Severe injury	17 (13)
Time (months) to injury, mean (SD)	
Minor injury	13.7 (1.0)
Moderate injury	14.6 (1.0)
Severe injury	14.4 (1.0)

(Continued)

Table 4 (Continued).

Patients at Risk of Developing ID, n/N (%)^{a,c-e}	135/190 (71)
Patients who developed any ID	21 (16)
Mild ID	NR ^f
Moderate ID	3 (2)
Severe ID	3 (2)
Others ^g	15 (11)
Time (months) to ID, mean (SD)	
Mild ID	16.4 (1.1)
Moderate ID	16.6 (1.1)
Severe ID	16.4 (1.1)
Others ^g	15.6 (1.1)

Notes: Data reported for patients with an index date within 2016–2018. The proportions reported are based on the number of patients at risk of developing each outcome, except for the total number of patients evaluated where the proportions reported are based on the total population of patients with LGS. ^aIdentified utilizing ICD-9/10 diagnosis codes for injury/ID (Supplementary Tables 4 and 5). ^bInjuries include fracture, concussion, or face and mouth injuries. ^cPatients at risk were restricted to those without injuries/history of ID before the index date. ^dRepresents the number of unique patients in the cohort minus the number of patients with injury/ID before index date. ^ePatients could present with different ID severities (disease progression) at index period. ^fThe corresponding numbers could not be reported owing to patient confidentiality. ^gUnspecified severity.

Abbreviations: ICD-9/10, International Classification of Diseases Ninth/Tenth Revision; ID, intellectual disability; LGS, Lennox-Gastaut syndrome; NHID, National Health Insurance Database; NR, not reported; SD, standard deviation.

code.^{8,22–25} The PPV calculated by comparing valid, clinician-reviewed cases with the estimated cases from the identification algorithm within the CGRD was applied to the NHID to improve the accuracy of the prevalence and incidence estimates. The PPV-adjusted prevalence of 2.4 per 100,000 people, calculated herein for the total population in 2018, confirms that LGS is rare in Taiwan based on current national standards for rare diseases of less than 1 per 10,000.²⁶

The LGS prevalence for the total population reported here is at the lower end of the ranges reported more recently in Europe^{25,27–30} and in the USA.^{31,32} Since there are no reports of racial differences in the prevalence of LGS,³³ the wide range in values for LGS prevalence indicate the challenges in identifying LGS and the need for improved patient identification algorithms. Despite a comparable algorithm being used in this study, the PPV-adjusted prevalence in the NHID was lower than the prevalence of validated LGS in the CGRD. This discrepancy in disease prevalence has been noted before³⁴ and may be explained by the differing patient profiles or physician expertise. Whereas the NHID contains data from a broad range of non-specialist healthcare facilities,³⁵ the CGRD contains patients referred to advanced care and covers severe conditions.¹³ The CGRD also includes more pediatric inpatients than the NHID.¹³ The present analyses found that LGS prevalence in Taiwan varied by age group (pediatric [aged 0–18 years] and adults [aged >18 years]), which is in line with previous reports.²³ Reasons for these differences may include the nature of the disease (childhood onset with more younger newly diagnosed patients than older)^{36,37} and the increased mortality rate in childhood versus adulthood,⁴ reducing the number of patients surviving to adulthood. The PPV-adjusted incidence of LGS per 100,000 person-years reported here is lower than the incidence reported in the literature in Europe.^{38–40} Reasons for these differences are likely similar to those discussed for prevalence.

Patients with confirmed LGS in the NHID had longer times to LGS diagnosis than to first ASM treatment. In practice, LGS is challenging to characterize (eg not all LGS criteria are present at onset, and EEG patterns are heterogeneous and not specific to LGS),^{36,41,42} and many clinicians are unable to distinguish LGS from other childhood-onset severe epilepsies.¹ The long times from first epilepsy diagnosis to first ASM prescription may highlight the need for improved treatment care plans for some patients, but may also reflect an atypical disease course for others. For example, since

treatment necessitates two or more seizures, it is possible, for some individuals, that there was a prolonged period of seizure freedom following the first diagnostic seizure, resulting in a prolonged time to ASM treatment. Delays in ASM treatment and LGS diagnosis were less prominent in the CGRD versus NHID and may reflect the differences in the databases outlined above for prevalence and incidence. Specifically, the NHID captures the full picture of time to treatment and diagnosis since it includes all medical visits; in contrast, the CGRD, being restricted to data from the seven CGMHs, likely reflects a later stage in the disease course after patients have relapsed following their initial treatment, based on earlier interactions with physicians at pediatric epilepsy clinics. In this study, the results for patient hospitalizations (annual hospitalization rate per patient, and hospitalizations per year) are higher than in other studies in LGS conducted in Germany or the United Kingdom, likely reflecting the different methods used to identify LGS.^{25,27} High hospitalization rates for patients with LGS may be the result of seizures that caused falls, such as drop attacks that are frequent in patients with LGS,^{36,41,42} medication adjustments or surgery,^{7,36} or due to the management of co-occurring symptoms such as behavioral or cognitive disorders.^{1,36,41} Future studies are required to determine the prevalence and association of these factors with epilepsy-related hospitalizations. In the present study, mean LOS for hospital admissions was 11.8 days, with around half of admissions lasting between 1–6 days and the other half 7 days or more. Other studies in LGS have reported variable data for mean LOS.^{25,27} Overall, our results are aligned with the literature in suggesting that there is an unmet need to reduce patient hospitalizations and alleviate the burden of illness for patients with LGS.

Overall, the healthcare costs here are consistent with published data.^{2,23–25} In both databases, a large proportion of the medication costs were attributable to ASMs, and inpatient costs were higher than outpatient costs. Current treatment guidelines recommend valproate as first-line treatment (plus lamotrigine or rufinamide), followed by clobazam, topiramate, or felbamate.^{7,43} Levetiracetam, perampampanel, zonisamide, and cannabidiol are recommended subsequent therapies.^{7,43} Our findings suggest that the most commonly used ASMs (valproate and levetiracetam) in patients with LGS were consistent with other studies in Taiwan for epilepsy,^{16,44} and in Asia, Europe, and North and South America.^{5,8,25,27} Given that patients in the NHID were treated for epilepsy several years prior to diagnosis of LGS, the more common usage of later-line (eg topiramate, clobazam) versus second-line (eg lamotrigine, rufinamide) therapies likely reflects the need for monitoring polypharmacy³⁶ and a population that has exhausted initial treatment options in early childhood. Indeed, the treatment-refractory nature of the epilepsy may have prompted physicians to examine the diagnosis more closely and may explain the later diagnosis of LGS for some patients.

In this study, mortality was evaluated over a short period (3 and 5 years in the NHID and CGRD, respectively) and few deaths were recorded in patients with confirmed LGS. Nevertheless, the mortality rates here were lower than those reported in the United Kingdom,²⁷ and the different access to healthcare between countries may be one reason for this discrepancy, although longer studies are needed. The Taiwanese healthcare system is easily accessible, and specialist care is not restricted.³⁵ Additionally, patients with rare diseases in Taiwan have easy access to financial subsidies (70–100% reimbursement of orphan drugs) following the Rare Disease and Orphan Drug Act in 2000, as well as having support from advocacy groups.^{45,46} These points highlight the importance of healthcare system accessibility, including unrestricted access to specialist care, and the role of financial support for patients with LGS in improving seizure control that potentially impacts mortality rates.

Strengths and Limitations

Our results were derived from patient records extracted from a nationwide database, strengthened by standardized clinical data with manual clinical review and case validation. The PPV-adjusted prevalence, based on the clinical validation step in the patient identification algorithm using EMR data, is unique and further contributes to a more accurate estimate of LGS prevalence. In addition to the missingness of data, inherent to retrospective EMR-based studies, this study has limitations of which we highlight 4. First, comparison with studies in Western populations is limited by different patient characteristics, follow-up periods, treatment guidelines, and reimbursement policies. There has been a wide range of reported LGS prevalence,^{2,3} highlighting the differences between study populations and countries. However, we have highlighted that the burden of illness of LGS was multifaceted based on epidemiologic parameters. Second, issues remain with patient coding accuracy, as discussed in the published literature.²⁷ The disease is challenging to characterize, leading to inexact estimation of LGS prevalence. In this study, patients were identified by LGS ICD-10

coding or by rufinamide prescription as a surrogate for LGS diagnosis. Further, patient cases (including those with probable LGS diagnosis based on broader criteria) were also clinically evaluated and validated by expert clinicians and a validation algorithm. This helped identify patients who were either not coded with LGS (eg those coded with epilepsy) or had LGS but were not prescribed with rufinamide. In the present study, only 52% from the NHID received a rufinamide prescription, highlighting the need to promote its use for better disease management. With the increased adoption and/or evolution of ICD codes, as well as improvement in the diagnosis accuracy, future studies may report more refined prevalence of LGS. Third, NHID is a claims database with several limitations such as lack of laboratory data and information on disease severity;^{12,47} these may limit the accuracy of prevalence estimates. While this study used the NHID, the results were validated by the CGRD, specifically the use of the PPV to increase the accuracy of the prevalence and incidence estimates – most notably for probable LGS cases. Finally, although the validated LGS cases from the 7 CGMHs in the CGRD¹³ may limit generalizability to the wider patient population (eg cases captured earlier in the disease course at pediatric clinics), the NHID results are applicable to the Taiwanese population at a nationwide level, representing all possible healthcare interactions. Variation in the incidence and prevalence of epilepsy within Taiwan has been reported,¹⁰ indicating that prevalence of LGS might also differ geographically. Differences in disease severity and co-occurring symptoms of patients (eg behavioral and cognitive impairments), and loss of follow up in the CGRD (when patients visit medical facilities outside the CGMH)^{13,34,48} also limit comparisons between databases.

Conclusions

In Taiwan, the burden of illness in patients with LGS is multifaceted, with inpatient and epilepsy-specific care being key drivers of costs and hospitalizations. LGS prevalence and incidence were lower than previously reported in other countries. This may reflect differences in diagnostic practices, coding accuracy, or study methodologies, all of which contribute to the broader issue of challenges in the timely diagnosis and treatment of patients with LGS. Improved epilepsy control may also reduce hospitalizations and LOS to decrease LGS expenditure. This study provides important information for future studies, and our patient identification algorithm could serve as an example for future LGS epidemiological studies.

Abbreviations

ASM, antiseizure medication; ATC, Anatomical Therapeutic Chemical; CGMH, Chang Gung Memorial hospitals; CGRD, Chang Gung Research Database; EEG, electroencephalogram; EMR, electronic medical record; HCRU, health-care resource utilization; ICD-9, International Classification of Diseases Ninth Revision; ICD-10, International Classification of Diseases Tenth Revision; ID, intellectual disability; LGS, Lennox-Gastaut syndrome; LOS, length of stay; NA, not available; NHID, National Health Insurance Database; NTD, New Taiwan dollar; NR, not reported; PPPY, per patient per year; PPV, positive predictive value; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Data Sharing Statement

All relevant data are provided with the manuscript and supporting files. Access to the patient-level dataset is not permissible.

Ethical Approval

This study was approved by the National Cheng Kung University Governance Framework for Human Research Ethics (approval number NCKU HREC-E-110-206-2) and the Chang Gung Medical Foundation Institutional Review Board (IRB; IRB number 202101560B0). As only retrospective and de-identified data were collected, informed consent was not sought from patients. The design and execution of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.⁴⁹

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

ASHY reports personal fees from Prospection, during the conduct of the study. CCW declares payment/honoraria for lectures, presentations, speakers bureaus from Chang Gung Medical hospital; WWS and MHK are former employees of Prospection; SB holds stocks or stocks options from Jazz Pharmaceuticals, Inc. The authors report no other conflicts of interest in this work.

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