Mortality Rates and Risk Factors Among Patients With Lennox-Gastaut Syndrome or Dravet Syndrome

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Introduction

- Patients with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) are at risk of premature mortality.[1]
- Previous studies have reported DS mortality rates per 1000 person-years (PY) of 15.8,[2] 1.7,[3] and 8.6,[4] with a median age at death of 4.7-7 years.[1]
- However, there are limited mortality data in LGS.
  - Few heterogenous studies with different populations and data sources reported varying mortality data.[1,5-8]
  - One UK study of 256 patients with LGS reported a mortality rate per 1000 PY of 6.1 (in those with confirmed LGS) and 4.2 (in those with probable LGS); median age at death was 26 years (confirmed) and 16 years (probable).[5]

Objective

- To examine mortality rates and patient-related characteristics in patients with LGS or DS using a US claims database linked with a mortality database.

Methods

- This retrospective study used the Komodo database from 1/1/2015-12/31/2024.
- Patients were included if they had ≥2 LGS (International Classification of Diseases [ICD]-10, G40.81) or DS (ICD-10, G40.83) claims ≥1 month apart in the patient qualification period (1/1/2015-12/31/2023) and 12 months of pre-index data.
- The index date was 1/1/2018 or the second LGS or DS claim date (if claim date ≥30 days after first claim), whichever occurred later.
- Study exit date was date of death, last recorded claim, or study end date of 12/31/2024, whichever occurred first.
- The primary endpoint was to evaluate LGS and DS mortality rates and standardized mortality ratios (SMRs).
- The secondary endpoint was to evaluate demographic and clinical characteristics associated with mortality.
- LGS and DS mortality rates per 1000 PY and SMRs were stratified by age (pediatric vs adult) and healthcare resource utilization (HCRU) severity score.
- HCRU severity score is a weighted composite score of several HCRU elements, including number of emergency room visits, hospitalizations, generalized tonic-clonic seizure claims, status epilepticus claims, and number of rescue medications, that reflects severity of background disease despite being unvalidated.
- Kaplan–Meier survival analysis was used to describe age-related survival probability.
- A Cox proportional hazards model was used to evaluate the association between mortality and demographic and clinical characteristics.

Results

- Overall, 33,404 and 2781 patients with LGS and DS were identified, respectively (**Table 1**).
- In DS, there was a greater proportion of deceased females compared with males (57.6% vs 42.4%, respectively).
  - In both the LGS and LGS populations, a numerically higher mean Area Deprivation Index (ADI) was reported for deceased patients compared with those who were alive.

Table 1. Baseline characteristics and demographics

	LENNOX-GASTAUT SYNDROME		DRAVET SYNDROME	
	ALIVE (n=31,329)	DECEASED (n=2075)	ALIVE (n=2722)	DECEASED (n=59)
Gender, n (%)				
Male	17,673 (56.4)	1166 (56.2)	1385 (50.9)	25 (42.4)
Female	13,656 (43.6)	909 (43.8)	1337 (49.1)	34 (57.6)
Race/ethnicity, n (%)				
Non-Hispanic White	13,372 (42.7)	1147 (55.3)	1101 (40.4)	26 (44.1)
Asian or Pacific Islander	959 (3.1)	31 (1.5)	111 (4.1)	3 (5.1)
Hispanic or Latino	4762 (15.2)	183 (8.8)	387 (14.2)	4 (6.8)
Black or African American	3086 (9.9)	195 (9.4)	211 (7.8)	8 (13.6)
Unknown/other	9150 (29.2)	519 (25)	912 (33.5)	18 (30.5)
HCP tier, n (%)				
1: Center of excellence	12,025 (38.4)	776 (37.4)	1272 (46.7)	27 (45.8)
2: Epileptologist	6180 (19.7)	375 (18.1)	526 (19. 3)	10 (16.9)
3: Neurology/child neurology	8629 (27.5)	663 (32.0)	613 (22.5)	12 (20.3)
4: Other	4495 (14.3)	261 (12.6)	311 (11.4)	10 (16.9)
Insurance, n (%)				
Medicaid	23,251 (74.2)	1580 (76.1)	1914 (70.3)	42 (71.2)
Medicare	3117 (9.9)	339 (16.3)	106 (3.9)	7 (11.9)
Commercial and other	4961 (15.8)	156 (7.5)	702 (25.8)	10 (16.9)
Area Deprivation Index, mean (n)	47.7 (29,174)	52.7 (1973)	46.2 (2572)	54.1 (58)

HCP, healthcare provider.

Overview

QUESTION

What are the mortality rates, standardized mortality ratios, and mortality-related patient characteristics in patients with LGS or DS?

INVESTIGATION

- A retrospective analysis using the US Komodo Healthcare claims database examined mortality data for patients with LGS or DS from January 1, 2015, to December 31, 2024.
- Patients were included if they had ≥2 LGS or DS claims ≥1 month apart in the patient qualification period and 12 months of pre-index data.
- The index date was January 1, 2018, or the second LGS or DS claim date (if claim date ≥30 days after first claim), whichever occurred later (based on availability of mortality data from Komodo).
- Study exit date was date of death, last recorded claim, or study end date of December 31, 2024, whichever came first.
- The primary endpoint was to evaluate LGS and DS mortality rates.
- The secondary endpoint was to evaluate demographic and clinical characteristics associated with mortality.

RESULTS

- Overall, 33,404 patients with LGS and 2781 patients with DS were identified.
- Mortality rates (95% CI) per 1000 PY in LGS and DS were 14.2 (13.6, 14.8) and 7.3 (5.6, 9.4), respectively.
- SMRs were 7.5 (7.2, 7.8) and 7.8 (6.0, 10.1), respectively.
- Mortality rates for pediatric vs adult patients and patients with high vs low HCRU severity scores are shown in **Figure A**.
- SMRs showed an increased risk of mortality in pediatric patients compared with the general population matched for age and sex.
- Comorbidities with a significant effect on mortality risk, including sleep apnea, GI issues, and wheelchair use, are shown in **Figure B**.

Figure A. Summary of mortality rate in DS and LGS

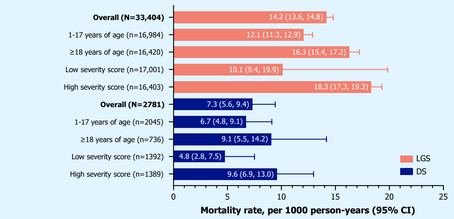
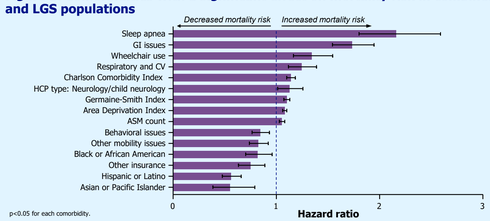


Figure B. Comorbidities with a significant effect on mortality risk in combined DS and LGS populations



p<0.05 for each comorbidity.

CONCLUSIONS

- In one of the largest real-word studies to date describing mortality rates in LGS and DS, we show high mortality in a large population of patients with LGS or DS, including pediatric and adult populations.
- Standardized mortality rates show patients with LGS or DS have an elevated risk of mortality compared with the general population, especially in pediatric patients.

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Abbreviations: ASM, antiseizure medication; CV, cardiovascular; DS, Dravet syndrome; GI, gastrointestinal; HCP, healthcare practitioner; HCRU, healthcare resource utilization; LGS, Lennox-Gastaut syndrome; PY, person-years; SMR, standardized mortality ratio.

- Clinical characteristics such as comorbidities, past medical history, and use of antiseizure medications (ASMs) were also reported (**Table 2**).
  - In LGS and DS, deceased patients experienced more sleep apnea, GI issues, cardiovascular/respiratory issues, and wheelchair use, and had higher mean Charlson Comorbidity Index and Germaine-Smith Comorbidity Index values, compared with those who were alive.

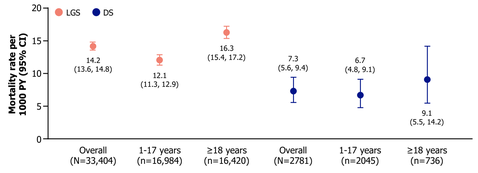
Table 2. Comorbidities, treatment history, and ASM use

	LENNOX-GASTAUT SYNDROME		DRAVET SYNDROME	
	ALIVE (n=31,329)	DECEASED (n=2075)	ALIVE (n=2722)	DECEASED (n=59)
Comorbidity and other treatment history, n (%)				
Sleep apnea[a,b]	6171 (19.8)	613 (29.6)	327 (12.1)	12 (20.3)
Other sleep issues[a,b]	2489 (8.0)	160 (7.7)	205 (7.6)	10 (16.9)
GI issues[a,b]	17,706 (56.9)	1587 (76.6)	1100 (40.8)	39 (66.1)
Behavioral issues[a,b]	9279 (29.8)	670 (32.3)	851 (31.6)	23 (39.0)
Cardiovascular and respiratory issues[a,b]	16,438 (52.8)	1435 (69.2)	1420 (52.7)	42 (71.2)
Wheelchair use[a,b]	1897 (6.1)	243 (11.7)	33 (1.2)	4 (6.8)
Other mobility issues[a,b]	6297 (20.2)	444 (21.4)	523 (19.4)	17 (28.8)
Developmental issues[a,b]	23,016 (74.0)	1648 (79.5)	1858 (68.9)	40 (67.8)
VNS/DBS	5333 (17.0)	398 (19.2)	413 (15.2)	9 (15.3)
Epilepsy surgery	315 (1.0)	11 (0.5)	16 (0.6)	0
HCRU Severity Score[c], mean	98.7	145.4	131.8	147.2
Charlson Comorbidity Index, mean	0.8	1.3	0.28	0.97
Germaine-Smith Comorbidity Index, mean	0.7	1.4	0.4	1.2
Number of unique ASMs in the baseline period, mean	2.2	2.5	2.3	3.0
Rescue medication claims in baseline period, mean	0.8	1.0	2.1	2.9

[a]In DS, data were missing for 25 patients in the alive subgroup.
[b]In LGS, data were missing for 206 patients in the alive subgroup and 2 patients in the deceased subgroup.
[c]A composite weighted score that has not been previously validated. The following HRCU weights were assigned: ER visit, 10 points per ER visit; inpatient admissions, 5 points per day of length of stay; any GTCS claim, 4 points per GTCS claims; any SE claims, 5 points per SE claim; ASM, 2 points for every distinct ASM molecule; rescue medication, 4 points for every claim of rescue medication. (Note: If a patient had an ER visit for SE, the points for both the ER visits and the SE claim were counted).
ASM, antiseizure medication; DBS, deep brain stimulation; DS, Dravet syndrome; ER, emergency room; GI, gastrointestinal; GTCS, generalized tonic-clonic seizure; HCRU, healthcare resource utilization; LGS, Lennox-Gastaut syndrome; SE, status epilepticus; VNS, vagus nerve stimulation.

- Mortality rates (95% CI) in LGS and DS were 14.2 (13.6, 14.8) and 7.3 (5.6, 9.4) per 1000 PY, respectively; mortality rates in children and adults are shown in **Figure 1**.

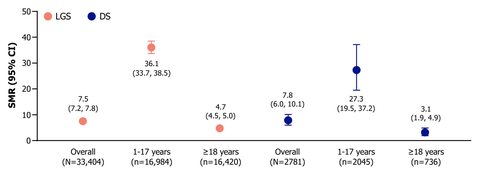
Figure 1. LGS and DS mortality rates per 1000 person-years



DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; PY, person-years.

- LGS and DS SMRs (95% CI) were 7.5 (7.2, 7.8) and 7.8 (6.0, 10.1), respectively (**Figure 2**).
- In both LGS and DS, SMRs were higher in pediatric vs adult patients (**Figure 2**).

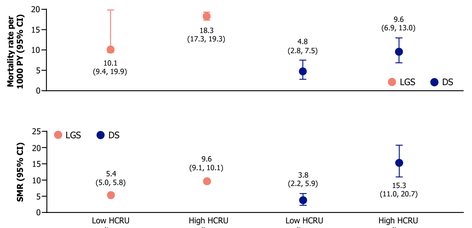
Figure 2. Standardized mortality rate of adult and pediatric patients with LGS and DS



DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; SMR, standardized mortality ratio.

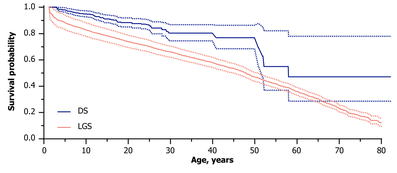
- A trend for higher mortality rates and SMRs was observed in patients with higher HCRU severity scores (**Figure 3**).

Figure 3. LGS and DS mortality rates per 1000 person-years and SMRs by HRCU severity score



DS, Dravet syndrome; HCRU, healthcare resource utilization; LGS, Lennox-Gastaut syndrome; PY, person-years; SMR, standardized mortality ratio.

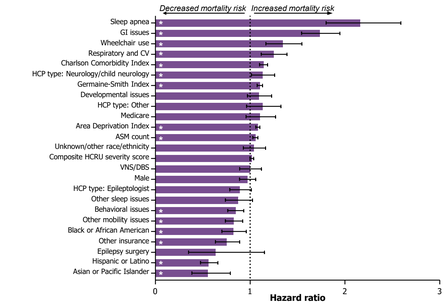
Figure 4. Age-related survival probability



Dashed lines represent 95% CIs.
DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

- For the total cohort including the LGS and DS populations, the Cox Proportional Hazards model indicated associations with mortality ($p<0.05$) for comorbidities such as sleep apnea, gastrointestinal issues, wheelchair use, and cardiovascular/respiratory issues; for Charlson and Germaine-Smith Comorbidity Indices; and for demographic characteristics such as ADI and certain races/ethnicities (**Figure 5**).

Figure 5. Comorbidity and mortality risk in combined LGS and DS populations



*p<0.05. Reference categories for categorical variables were HCPs at centers of excellence for HCP type, Medicaid for insurance type, and Non-Hispanic White for race/ethnicity. Comorbidities, epilepsy surgery, and VNS/DBS were yes/no categorical variables.
ASM, antiseizure medication; CV, cardiovascular; DBS, deep brain stimulation; DS, Dravet syndrome; GI, gastrointestinal; HCP, healthcare professional; HCRU, healthcare resource utilization; LGS, Lennox-Gastaut syndrome; VNS, vagus nerve stimulation.

Conclusions

- Here, we present one of the largest real-word studies to date describing mortality rates and SMRs in the LGS and DS populations.
- In DS, mortality rates and SMRs reflect those previously reported in literature.
  - In this study, DS mortality rates per 1000 PY (7.3) align with a previous report by Donnan et al 2023[4] (8.6) and a specialty US pharmacy study (8.0).[9]
- In LGS, mortality rates per 1000 PY (14.2) were higher when compared with a previous UK study with a smaller sample size (6.1).[5]
- In LGS and DS, we observed higher mortality rates and SMR in patients with higher HCRU severity scores and higher SMR in pediatric patients.
- ADI and clinical factors such as number of unique ASMs in the pre-index period; comorbidities such as sleep apnea, gastrointestinal issues, wheelchair use, and respiratory and cardiovascular comorbidities; and higher composite comorbidity scores were significantly associated with higher mortality risk.
- This study highlights the risk of premature mortality in patients with LGS or DS, and in those with high severity due to specific mortality and demographic and clinical characteristics.

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