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

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ABSTRACT

Objective: Ten-year retrospective study to assess burden of illness in patients with probable Dravet syndrome (DS) identified from German healthcare data.
Methods: In the absence of an International Classification of Diseases code, patients with probable DS were identified using a selection algorithm considering diagnoses and drug prescriptions. Primary analyses were prevalence and demographics; secondary analyses included healthcare costs, annual hospitalization rate (AHR) and length of stay (LOS), medication use, and mortality.
Results: In the final study year, 64 patients with probable DS (mean [range] age: 33.2 [3–82] years; male: 48%) were identified. Prevalence: 4.7 per 100,000 people. During the study, 160 patients with probable DS were identified and followed up for 1,261 patient-years. Mean cost of healthcare was €11,048 per patient-year (PPY), mostly attributable to inpatient care (47%), medication (26%), and services and devices (19%). Annual healthcare costs were significantly greater for those with prescribed rescue medication (15% of patient-years) vs. without (€16,123 vs. €10,125 PPY, $p < 0.001$). Mean (standard deviation [SD]) AHR and LOS were 1.1 (1.7) and 17.5 (33.5) days PPY. AHR was significantly greater in patients with prescribed rescue medication vs. without (1.6 [2.0] vs. 1.0 [1.6] PPY, $p < 0.001$). Mean (SD) number of antiseizure medications prescribed was 2.6 (1.2) PPY and 5.0 (2.5) over the entire observable time for each patient. Mortality rate was significantly higher for probable DS vs. matched controls (11.88% [19 events] vs. 1.19% [172 events], $p < 0.001$).
Conclusion: Probable DS is associated with substantial healthcare costs in Germany.

1. Introduction

Dravet syndrome (DS) is a rare form of epilepsy that principally manifests itself within the first year of life in an otherwise healthy child, typically with prolonged febrile seizures or status epilepticus (SE) [1]. Generalized convulsive seizures are predominant during the first year, although multiple seizure types occur over time [1,2]. DS is considered to be one of the most challenging epileptic encephalopathies and is associated with developmental delay and behavioral disorders [1,3]. Comorbidities include cognitive impairment, autism spectrum disorder, neuropsychiatric abnormalities, and motor impairment [1,2]. Early treatment of seizures may reduce their effects on the developing brain [2], although

Abbreviations: AHR, annual hospitalization rate; ASM, antiseizure medication; ATC, Anatomical Therapeutic Chemical; CI, confidence interval; DEE, developmental epileptic encephalopathy; DS, Dravet syndrome; GKV, Gesetzliche Krankenversicherung; ICD-10, International Classification of Diseases 10th Revision; ICD-10-GM, International Classification of Diseases 10th Revision, German modification; LGS, Lennox–Gastaut syndrome; LOS, length of stay; NA, not applicable; PPY, per patient-year; Q1–Q3, interquartile range; SD, standard deviation; SE, status epilepticus; SUDEP, Sudden Unexpected Death in Epilepsy; TSC, tuberous sclerosis complex.

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many patients receive polypharmacy without adequate seizure control [1,4]. Patients with DS have a high epilepsy-related premature mortality rate (3.7–20.8%) [5–7], mostly as a result of Sudden Unexpected Death in Epilepsy (SUDEP) or SE [8]. Moreover, the mortality rate in patients with DS is greater than that reported in a cohort of patients aged ≤18 years admitted to hospital with SE (3.0%) [9].

DS is associated with a range of difficulties that affect patients, families, and caregivers. Patients experience poor social and school function as children, with negative impacts on speech and communication that persist into adulthood [10]. Supporting a patient with DS can place a substantial strain on caregivers, commonly resulting in anxiety, depression, financial insecurity, limited career progression, and emotional stress [10–12].

Analyses of the burden of illness associated with DS have largely focused on indirect costs, such as loss of productivity [11,13]. Direct healthcare cost data for DS have mostly been obtained from questionnaire-based studies [11–13] or retrospective patient record review [14]. The single published health insurance claims analysis in patients with DS was based on US data [15]. The scarcity of healthcare database cost analyses is due to both the low prevalence of DS and a lack of appropriately captured healthcare information. Prior to October 2020, the International Classification of Diseases 10th Revision (ICD-10) did not include a specific code for DS. In the absence of an ICD-10 code, healthcare database analyses can be conducted using patient selection algorithms to identify patients with probable DS.

The objective of this retrospective study was to examine the epidemiology, healthcare cost and utilization, medication use, comorbidities, injuries, and mortality for patients with probable DS using information from a German healthcare insurance claims database. Data from a 10-year period between January 1, 2007 and December 31, 2016 were assessed.

2. Materials and methods

2.1. Data source

This study utilized healthcare insurance claims data obtained from the Vilua Healthcare research database, which represents approximately 5% of the German population covered by statutory health insurance ('Gesetzliche Krankenversicherung'; GKV). This database was used for similar studies in probable Lennox–Gastaut syndrome (LGS) [16] and tuberous sclerosis complex (TSC) [17].

The study was approved by the ethics committee of the University of Frankfurt, Germany. Written informed consent from participants was waived because this was a non-interventional study using anonymized patient data.

2.2. Identification of patients with probable DS

During the study period, there was no DS-specific ICD-10 code. In order to retrieve patients most likely to have a diagnosis of DS, while excluding those with other neurological disorders, an identification algorithm was developed (Fig. 1). This selected patients with ≥1 ICD-10 diagnosis of G40 (epilepsy)/G41 (SE) and ≥1 prescription of stiripentol or potassium bromide (identified in the context of the epilepsy diagnosis). Stiripentol was chosen because it is only indicated for use as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with DS in conjunction with clobazam and valproate [18], and it is a mainstay of treatment for DS in the European Union [19]. Potassium bromide was included in the algorithm as it is commonly used in Germany to treat DS [19]. If there was no prescription of stiripentol or potassium bromide, a previous combination of valproate and clobazam

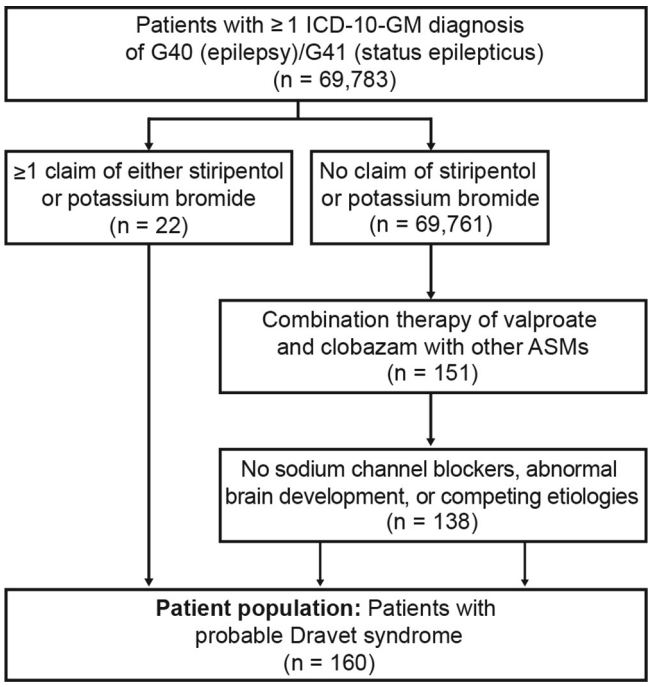

Fig. 1. Patient selection process for probable DS. ASM, antiseizure medication; DS, Dravet syndrome; ICD-10-GM, International Classification of Diseases 10th Revision, German modification.

with other antiseizure medications (ASMs), commonly referred to as antiepileptic drugs, was required for inclusion. Valproate and/or clobazam are considered first-line therapies for DS [2,3,20]. Patients with the specified ASM combination therapy were excluded if there was any use of sodium channel blockers (carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, lacosamide, rufinamide, lamotrigine, or felbamate), abnormal brain development, or competing etiologies such as TSC [17] or probable LGS [16]. ICD-10 codes used for this study are listed in Supplementary Table 1. The algorithm was considered appropriate to identify patients with DS since the 4 most commonly used ASMs in patients

Table 1
Epidemiology of patients with probable DS in 2016.

	Patients identified with probable DS	
Number of patients, n (%)	64 (100)	
Mean age, years	33.2	
Prevalence[a] (per 100,000 people)		
Unstandardized to German GKV population	4.8	
Standardized to German GKV population	4.7	
Sex distribution per age group, n (%)		
Age range (years)	Male	Female
0–1	0	0
2–9	5 (16)	6 (18)
10–19	4 (23)	3 (9)
20–29	12 (29)	3 (9)
30–39	1 (3)	5 (15)
40–49	4 (13)	4 (12)
50–59	2 (6)	6 (18)
60–69	2 (6)	4 (12)
70–79	1 (3)	1 (3)
80+	0	1 (3)

DS, Dravet syndrome; GKV, Gesetzliche Krankenversicherung (statutory health insurance).

[a] Prevalence calculations are based on all patients, including those who changed insurance company or died during an observation year (n = 65); 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 [n = 64]).

with DS in Germany are valproate, potassium bromide, clobazam, and stiripentol [19]. In combination, the presence of typical ASMs, the absence of structural brain abnormalities, and the exclusion of patients with probable LGS or TSC resulted in a population of patients with DS or a comparable developmental epileptic encephalopathy (DEE).

2.3. Outcomes

Primary analyses were prevalence, and age and sex distribution based on patients identified in the final year of the study (2016), which was chosen in order to obtain the most accurate and recent epidemiological data. Secondary analyses were annual healthcare costs, annual hospitalization rate (AHR) and length of stay (LOS, days, calculated at discharge), medication use, comorbidities, injuries, and mortality. Secondary analyses were assessed using patients identified across the entire study (2007–2016). 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.

The cost of illness associated with probable DS 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. Costs (Euros, €) were adjusted to the 2015 price year using the German Health Consumer Price Index [21]. Cost data by age were evaluated over 10-year periods and recorded annually according to age at the time of assessment. Costs for patients with no recorded hospital admittances and associated costs over a year were recorded as €0. AHR and LOS were calculated for all patients, patients hospitalized due to primary probable DS diagnosis, and patients hospitalized with mechanical ventilation.

The number of different medications was determined from the number of different Anatomical Therapeutic Chemical (ATC) Classification System codes noted throughout the study for each patient. The most commonly prescribed ASMs (ATC code N03A + clobazam N05BA09) were assessed using the data for each patient in their last observation year (either the final year of the study or the year in which the patient left the database). Injuries and mortality in patients with probable DS were compared with age- and sex-matched (standardized) controls without probable DS, probable LGS, or TSC over an equal observation time. To generate the control groups, the database was searched for as many patients as possible who were of the same age and sex, and with at least an equal observation time, as each patient with probable DS. Patients with probable LGS or TSC were excluded from the control groups because this analysis of patients with probable DS was part of a larger study that identified populations with one of these 3 conditions [16,17].

Subgroup analyses of cost, AHR, LOS, and mortality data were conducted based on prescription of rescue medication, defined as ≥1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate in ≥1 year during the study period (all parameters) or during the year that they were identified with probable DS (mortality only). This analysis was prompted by the observation that patients who received rescue medication experienced more seizures and were prescribed more ASMs than those with no rescue medication use [22].

2.4. Statistical analysis

Data were analyzed with the Structured Query Language server 2016 SP2, R 3.6.2, and Microsoft Excel. P-values were derived from a t-test hypothesizing that the mean costs (per setting) of patients prescribed with rescue medication were equal to the mean costs (per setting) of patients without prescribed rescue medication. Relative risks (RR) to comparator groups were calculated for injuries and mortality data. P-values were derived from a log-rank test (using chi-squared distribution) to assess the significance of mortality data vs. standardized controls.

3. Results

3.1. Patient demographics and characteristics

Using data from 2016, the algorithm identified 64 patients with probable DS (Table 1). The prevalence (age and sex standardized to German GKV population) was 4.7 per 100,000 people. Mean (range) age was 33.2 (3–82) years; 48% of patients were male.

During the 10-year study period (January 1, 2007 to December 31, 2016), 160 patients with probable DS were identified and followed up for 1261 patient-years. Few patients (n = 22) were identified by prescription of stiripentol or potassium bromide; the remaining 138 patients were identified by a combination of valproate and clobazam with other ASMs. Less than half of patients (63/160, 39%) were prescribed rescue medication on at least 1 occasion during follow-up.

3.2. Healthcare costs

3.2.1. All patients

During the 10-year study period, the mean annual cost of healthcare was €11,048 per patient-year (PPY; Table 2) and was mostly attributable to inpatient care (47%), medication (26%), and services and devices (19%). Inpatient costs resulting from hospital stays related to epilepsy were high (€4,471 PPY). ASMs were responsible for 37% of the medication costs. In addition, almost all patients (139/160) received anxiolytics (mostly benzodiazepines), resulting in 1,932 prescriptions at a mean cost of €24 per prescription. The most commonly prescribed benzodiazepines were clobazam (121/160 patients, 76%), diazepam (68, 43%), and lorazepam (65, 41%). In total, 743 prescriptions of antipsychotics were made to 35 patients (mean cost €129 per prescription); the most commonly prescribed (≥5% of patients) were risperidone (16, 10%), melperone (12, 8%), and quetiapine (9, 6%). High non-ASM medication costs were influenced by several expensive medications that were prescribed to a small number of patients over the study period, for example, other antineoplastic agents to 3 patients (total of 74 prescriptions at a mean cost of €3,345 per prescription), immunosuppressants to 3 patients (5 prescriptions, €5,073), and plant alkaloids and other natural products to 1 patient (4 prescriptions, €5,083).

3.2.2. Patients with prescribed rescue medication

Over the 10-year study period, rescue medication was prescribed at least once in 194/1,261 (15%) patient-years. The proportion of patient-years with prescribed rescue medication was lower in older age groups (Supplementary Table 2). Mean annual total healthcare costs were significantly greater in patients with prescribed rescue medication vs. those without (€16,123 vs. €10,125 PPY, $p < 0.001$; Table 2). Greater costs in patients with prescribed rescue medication than those without were seen across all categories, including inpatient care, medication, services and devices (most notably intensive nursing care and special equipment), and outpatient care. While medication costs represented a similar proportion of total costs in patients with and without rescue medication (25% vs. 26%), a greater proportion of medication costs was associated with ASMs in patients with prescribed rescue medication than those without (47% vs. 34%).

Table 2
Annual healthcare costs for patients with probable DS during the 10-year study period.

Patient-years	All patients		Years where patients prescribed with rescue medication[a]		Years where patients not prescribed with rescue medication[a]		*P*-value[b]
	1,261		194		1,067		
	Annual cost per patient-year, €						
	Mean	Median (Q1–Q3)	Mean	Median (Q1–Q3)	Mean	Median (Q1–Q3)	
Total	11,048	2,591 (0–12,071)	16,123	8,283 (0–20,905)	10,125	2,176 (0–9,664)	< 0.001
Inpatient	5,147	0 (0–2,695)	7,376	0 (0–5,757)	4,741	0 (0–2,308)	0.031
Epilepsy-related	4,471	0 (0–3,198)	7,029	1,360 (0–6,711)	3,984	0 (0–2,633)	0.016
Outpatient	754	250 (0–1,024)	1,103	545 (0–1,346)	690	230 (0–952)	0.008
Medication	2,826	623 (0–3,250)	4,104	1,752 (0–5,803)	2,594	495 (0–2,635)	0.004
ASMs	1,043	268 (1–673)	1,916	390 (20–1,294)	884	249 (0–603)	< 0.001
Sickness payment	254	0 (0–0)	7	0 (0–0)	299	0 (0–0)	< 0.001
Blood purification	24	0 (0–0)	0	0 (0–0)	28	0 (0–0)	0.202
Services and devices	2,044	0 (0–1,490)	3,533	1,191 (0–4,020)	1,773	0 (0–1,039)	0.021
Special equipment	113	0 (0–0)	224	0 (0–0)	92	0 (0–0)	0.082
Intensive home nursing care	83	0 (0–0)	542	0 (0–0)	0	0 (0–0)	0.319
Other physical therapies	66	0 (0–0)	127	0 (0–0)	55	0 (0–0)	0.136
Transport for medical needs	51	0 (0–0)	70	0 (0–0)	48	0 (0–0)	0.352
Physiotherapy	37	0 (0–0)	93	0 (0–0)	26	0 (0–0)	0.106
Home nursing care	22	0 (0–0)	32	0 (0–0)	20	0 (0–0)	0.612
Other costs	1,673	0 (0–959)	2,444	558 (0–3,382)	1,532	0 (0–696)	0.027

ASM, antiseizure medication; DS, Dravet syndrome; Q1–Q3, interquartile range.
[a]Rescue medication prescription is defined by having at least 1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate. [b] T-test for patients with rescue medication prescription vs. patients without rescue medication prescription.

3.3. Hospitalization rates and length of stay

3.3.1. All patients

During the 10-year study period, mean (standard deviation [SD]) AHR was 1.1 (1.7) with annual LOS of 17.5 (33.5) days PPY (Table 3). The range for AHR was 0–14 PPY; the range for LOS was also wide (0–236 days). The main reason for hospitalization was epilepsy and recurrent seizures (G40 ICD-10 code), occurring in 86% of patients, followed by SE (G41, 24%) and reaction to severe stress and adjustment disorders (F43, 6%).

3.3.2. Patients with prescribed rescue medication

Mean AHR and LOS were significantly greater in patient-years with prescribed rescue medication vs. those without (Table 3).

3.4. Medication use

During the 10-year study period, the mean (SD; median) number of different medications prescribed was 8.6 (5.4; 7.0) PPY and 28.7 (15.9; 24.0) over the entire observable time for each patient. ASMs accounted for a mean (SD; median) of 2.6 (1.2; 2) of the medications prescribed PPY and 5.0 (2.5; 4.5) over the entire observable time. Patients generally received between 1 and 3 different ASMs in each year (range: 1–7), and most patients received either 2, 3, or 4 different ASMs (23%, 33%, and 24%; range 1–9) over the entire observable time. During the last year of observation for each patient, the most commonly prescribed ASMs or ASM combinations (prevalence ≥5%; number of patients, %) were valproate (30, 21%); clobazam and valproate (21, 15%); lamotrigine

Table 3
AHR and LOS for patients with probable DS during the 10-year study period.

Number of patients, n (%)	All patients 160 (100)		Years where patients prescribed with rescue medication[a] 63 (39)		Years where patients not prescribed with rescue medication[a] 97 (61)		*P*-value[b]	
	AHR	LOS (days)	AHR	LOS (days)	AHR	LOS (days)	AHR	LOS
All patients								
Patient-years	1,261	1,261	194	194	1,067	1,067		
Mean (SD)	1.1 (1.7)	17.5 (33.5)	1.6 (2.0)	24.7 (40.5)	1.0 (1.6)	16.2 (32.0)	< 0.001	0.006
Median (range)	0 (0–14)	0 (0–236)	1 (0–8)	6 (0–234)	0 (0–14)	0 (0–236)		
95% CI	1.0–1.2	15.7–19.4	1.4–1.9	19.0–30.4	0.9–1.1	14.3–18.2		
All patients (due to primary probable DS diagnosis)								
Patient-years	1,261	1,261	194	194	1,067	1,067		
Mean (SD)	0.7 (1.4)	10.3 (25.1)	1.3 (1.9)	17.7 (30.6)	0.6 (1.3)	8.9 (23.8)	< 0.001	< 0.001
Median (range)	0 (0–13)	0 (0–235)	1 (0–10)	0 (0–182)	0 (0–13)	0 (0–235)		
95% CI	0.6–0.8	8.9–11.7	1.0–1.5	13.4–22.0	0.5–0.7	7.5–10.4		
Patients hospitalized with mechanical ventilation								
Patient-years	3	3	0	0	3	3		
Mean (SD)	1.0 (0.0)	10.0 (6.1)	–	–	1.0 (0.0)	10.0 (6.1)	–	–
Median (range)	1 (1–1)	13 (3–14)	–	–	1 (1–1)	13 (3–14)		
95% CI	1.0–1.0	3.1–16.9	–	–	1.0–1.0	3.1–16.9		

AHR, annual hospitalization rate; CI, confidence interval; DS, Dravet syndrome; LOS, length of stay; SD, standard deviation.
[a] Rescue medication prescription is defined by having at least 1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate. [b] T-test for patients with rescue medication prescription vs. without rescue medication prescription.

(13, 9%); clobazam, lamotrigine, and valproate (13, 9%); and lamotrigine and valproate (11, 8%). Patients identified by a combination of valproate and clobazam with other ASMs were excluded if any use of sodium channel blockers was noted at study entry. However, lamotrigine was prescribed at least once after probable DS diagnosis for 91 patients (57%), with almost half of these patients (44, 48%) receiving lamotrigine for up to 2 years. Few patients were prescribed stiripentol (7, 4.4%) or potassium bromide (7, 4.4%) during their last observation year, consistent with low use of these ASMs at study entry. Topiramate was prescribed for 15 patients (9%) during their last observation year. The 5 most commonly prescribed medications (number of patient-years, %) over the entire study period were valproate (724, 57%), lamotrigine (453, 36%), clobazam (433, 34%), levetiracetam (421, 33%), and ibuprofen (322, 26%).

3.5. Comorbidities

In their last year of observation, comorbidities were common in patients with probable DS, most notably respiratory infections (49%), injuries (42%), cognitive disabilities (42%), physical disabilities (24%), incontinence (21%), and artificial body orifices (9%). Over the entire study period, respiratory infections and injuries were each reported for 89% of patients, while cognitive disabilities were reported for 49% of patients.

3.6. Injuries

A greater proportion of patients with probable DS reported at least 1 injury during the 10-year study period than matched controls (87% vs. 58%; RR = 1.5); these were most commonly injuries to the trunk (61% vs. 39%; RR = 1.56) and head (58% vs. 18%; RR = 3.2). Epilepsy and recurrent seizures (G40) was the most frequently reported secondary diagnosis in all patients hospitalized due to a fracture (probable fall) during the study.

3.7. Mortality

3.7.1. All patients

Over the 10-year study period, mortality rate was significantly greater in patients with probable DS than matched controls (11.88% [19 events] vs. 1.19% [172 events], $p < 0.001$; RR = 9.98; Fig. 2A). Two of the patients with probable DS who died were aged <18 years (8 and 13 years), 2 were aged 18–39 years (26 and 34 years), and 15 were aged ≥40 years (mean 63 years; range 43–90 years). The mortality rate was similar in male (12.79% [11 events]) and female (10.81% [8 events]) patients (Fig. 2B), RR = 1.18.

3.7.2. Patients with prescribed rescue medication

The mortality rate was 7.94% (5 deaths in 63 patients) in patients with probable DS who were prescribed with rescue medication at least once during the study period vs. 14.43% (14 deaths in 97 patients) in those who were not prescribed rescue medication (RR = 0.55). The difference in mortality was statistically significant ($x^2 = 73.95$).

The mortality rate of patients who were prescribed rescue medication during the year that they were identified with probable DS (n = 34) was significantly greater than that of matched controls (8.82% [3 deaths] vs. 0.1% [3 deaths]; $p < 0.001$; RR = 882; Fig. 2C).

4. Discussion

This retrospective study presents an analysis of epidemiology, healthcare costs, hospitalizations, medication, and mortality using healthcare insurance data for patients with probable DS living in Germany. These data cover a 10-year period and are representative of the German population.

Using data from 2016, the selection algorithm identified 64 patients with probable DS resulting in a standardized prevalence of 4.7 per 100,000. Previous non-population-based analyses in the USA and France have suggested a similar prevalence of DS ranging from 1 in 40,000 (2.5 per 100,000) to 1 in 20,000 (5.0 per 100,000) [23,24]. However, these studies are over 20 years old and selected patients with a diagnosis of severe myoclonic epilepsy of infancy. Furthermore, non-population-based data are only reflective of those within the study and may not be applicable to the general population with DS.

A recent prospective epidemiological cohort study in Scotland reported an incidence of genetically confirmed *SCN1A*-related seizures of 8.26 per 100,000 live births [25]. Of the 14 patients identified with *SCN1A* variants, 11 were ultimately diagnosed with DS. A population-based study in the UK reported a lower prevalence of DS of 1 in 40,900 (2.4 per 100,000) [26]. It is notable that these 2 studies only selected patients with an *SCN1A* mutation, although patients with DS can be *SCN1A*-mutation negative [1]. Other population-based studies report similar prevalence data, including 1 in 33,000 live births (3.0 per 100,000) and 1 in 45,700 (2.2 per 100,000) in children aged <18 years in Sweden [27] and 1 in 15,700 (6.4 in 100,000) in the US [28]. All studies agree that DS is a rare disorder with a prevalence between 2.2 and 6.4 per 100,000. Most of the patients identified by our algorithm were adults. Since DS has only recently been described and defined, it is possible that some older patients may not have received a diagnosis. Using a DS-specific algorithm may thus be an appropriate approach for patient identification.

A lack of disorder awareness can hinder prevalence estimations in population-based studies of rare disorders such as DS. Increased awareness and knowledge of DS may lead to more referrals for genetic testing (*SCN1A* mutation) and, in turn, more accurate prevalence data [27]. The lack of a specific ICD-10 code for DS prior to October 2020 is a limitation of all retrospective analyses in this population that use healthcare databases.

The cost data reported in the present study agree with previously published analyses that the direct healthcare costs associated with DS are high [11–15,29–31]. Hospitalization and/or inpatient-related expenses represent the main proportion of the mean annual direct costs incurred by patients with DS [11–13,30]. Most European analyses used a questionnaire-based, bottom-up methodology, which may be susceptible to a participating center and patient selection bias. There is also the potential for recall bias if the responder is unable to remember details accurately. The present top-down analysis reports trends observed in healthcare insurance data over a period of 10 years and is not subject to the limitations of a survey-based analysis.

Indirect costs of DS were not captured by our analysis, but it has been reported that these are also high, illustrated by the relatively high proportion of parents who quit their job or retired early due to caregiving with substantial loss of income [12,13]. Thus, both direct and indirect cost analyses underline the considerable burden that DS places on patients and caregivers.

In our analysis, mean AHR was 1.1 PPY with a mean LOS of 17.5 days PPY. AHR and LOS were highly variable between patients, with a maximum of 14 hospitalizations PPY. The most common reason for hospitalization was epilepsy and recurrent seizures, occurring in 86% of hospitalized patients during the study and suggesting that seizure control is not adequate in many patients. The incidence of hospitalization due to SE (24%, defined as ICD-10 code G41) may have been underestimated since febrile SE can also be coded as R56 (febrile convulsions). These findings are in keeping

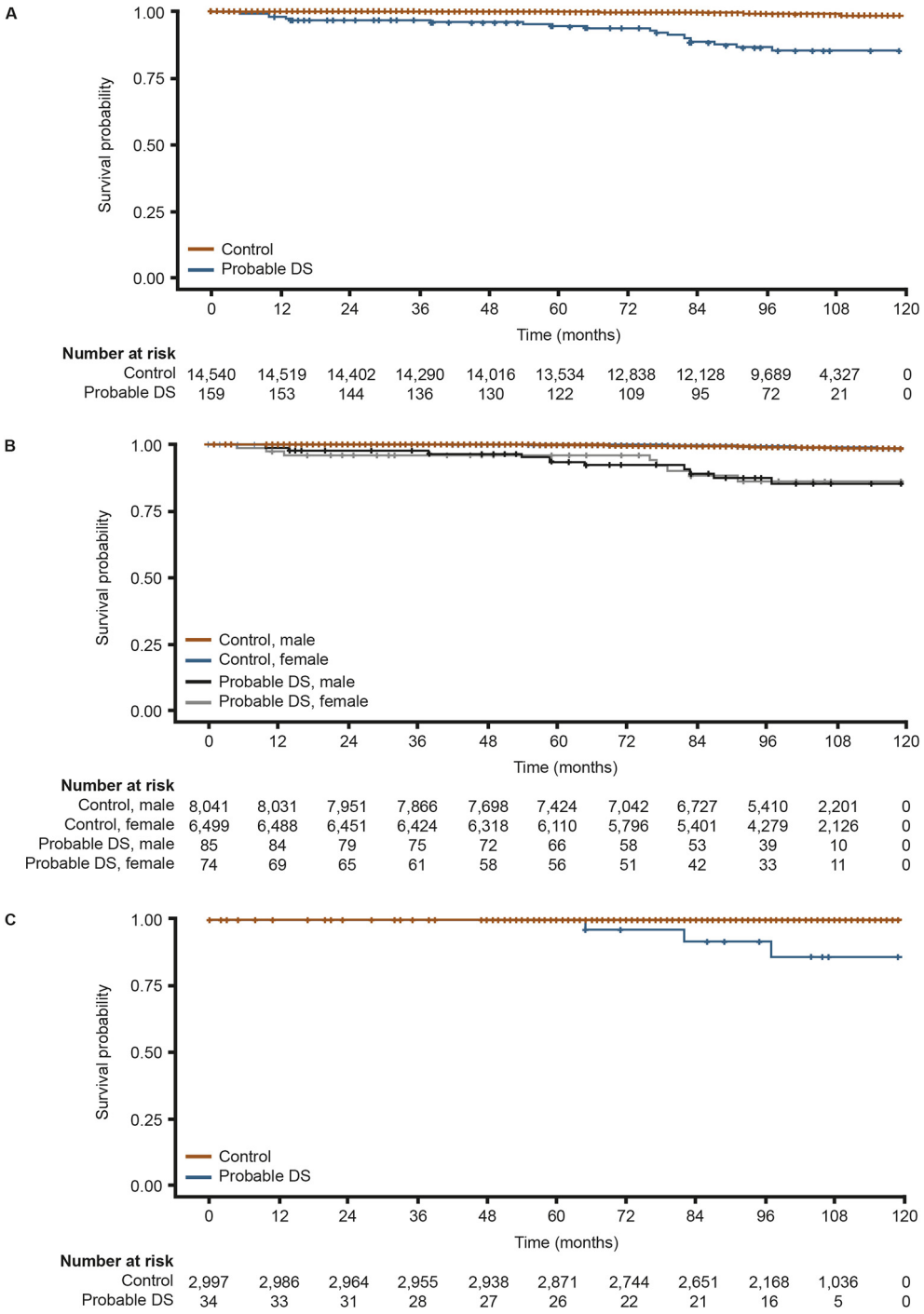

Fig. 2. Survival rate of patients with probable DS and matched controls[a] during the 10-year study period for all patients (A), all patients by sex (B), and patients prescribed rescue medication[b] (C). [a] The control group consists of individuals of same age and sex distribution over an equal observation time. [b] Rescue medication prescription is defined by having at least 1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate during the year in which they were identified with probable DS. One patient was excluded from the probable DS group (all patients) because of missing data. DS, Dravet syndrome.

with the treatment-resistant, debilitating seizure types that characterize DS [3].

Several other studies have reported hospitalization data for patients with DS, although direct comparisons are limited due to differences in methodology. Our findings are broadly consistent with a US study that reported mean inpatient admissions of 0.4–0.5 PPY for patients with probable DS [15]. A recent prospective and retrospective survey of the direct and indirect costs of DS in Germany reported that 52% of the study population had ≥1 inpatient visit in the 12-month period previous to the survey. Mean AHR among all patients who were hospitalized at least once was 4.3, with a mean LOS of 25.6 days [12].

SE is common in patients with DS; a survey of 274 European patients with DS noted that one-third of patients had at least 1 episode of SE requiring emergency room admission over the last year [32]. Guidelines recommend that all patients with DS have an

emergency care plan for prolonged or repetitive seizures, with benzodiazepines regarded as first-line rescue treatment for home use [3,20]. Surprisingly, rescue medication was prescribed relatively infrequently in the present study (≥1 prescription in 15% of patient-years). Midazolam, diazepam (rectal formulation), and chloral hydrate were counted as rescue medications since these are commonly used [19]. However, it is possible that some patients were prescribed other drugs, such as lorazepam or oral formulations of diazepam, as rescue medication. Most patients were prescribed benzodiazepines at least once; this may have been intended for use as rescue medication. In line with this, a survey in Germany found that slowly absorbed oral benzodiazepines, such as lorazepam, are frequently used as emergency medication in adults with epilepsy [22]. Oromucosal midazolam is only indicated for the treatment of prolonged, acute, convulsive seizures in patients aged <18 years [33], which may explain its low use in this, mainly adult, study population. The rescue medication population may thus have missed some patients who were prescribed medications not included in the above definition. Nevertheless, in planned subgroup analyses, patients with prescribed rescue medication were associated with significantly greater annual healthcare costs than those without (€16,123 vs. €10,125 PPY, $p = 0.001$), as well as significantly higher AHR and longer LOS. Patients with prescribed rescue medication may represent a group with frequent hospital admissions who are given rescue medication to reduce or avoid further hospitalizations.

The wide range of different medications prescribed over the study duration reflects the diversity of DS and its tendency to be challenging to treat [6,10,34,35]. The International League Against Epilepsy guidelines define drug-resistant epilepsy as failure of adequate trials of 2 tolerated, appropriately chosen and used ASM schedules, and research shows that the third and subsequent ASMs only have a modest probability of achieving seizure freedom [36]. In this study, patients typically received between 2 and 4 different ASMs over the study period. Similar findings have been reported across Europe [32] and in a previous German study [19]. In clinical practice, patients with DS usually remain on an ASM for at least 6 months, with dose increments as required up to a maximally tolerated dose, before considering discontinuing or adding another ASM. The most frequently prescribed ASM was valproate either as monotherapy or with clobazam, which is in keeping with current treatment guidelines for DS [3] and previous studies [10,19,32,37]. Lamotrigine was prescribed at least once for more than half of the patients during our study. Although sodium channel blockers are contraindicated in patients with DS [3] and particularly in children [2], case reports have suggested that lamotrigine may be beneficial in some patients with DS, and withdrawal in adults and adolescents who are established on lamotrigine may result in seizure exacerbation [38]. A recent retrospective study in Norway found that more than one-third of patients with DS had tried sodium channel blockers, including lamotrigine, although its use had declined over the past decade (between 2008/09 and 2017/18) [39].

Patients with DS are often subject to seizures that can cause significant injury, such as convulsive or atonic (drop) seizures [2]. At least 1 injury was reported by almost all (87%) patients with probable DS; head injuries were particularly frequent (58%; control: 18%).

In their last year of observation, the majority of patients in this study had other comorbidities in addition to epilepsy, most commonly respiratory infections (49%), cognitive disabilities (42%), and injuries (42%). However, the incidence of comorbidities documented in this population-based claims database study was lower than reported by caregivers in questionnaire-based studies [32,40]. Comorbidities such as delayed development may not be formally diagnosed and subsequently coded in a healthcare database. Caregiver questionnaires may thus be better able to reflect the breadth of cognitive and behavioral comorbidities associated with DS. When data were analyzed over the entire study period, the incidence of respiratory infections and injuries increased, while the incidence of cognitive disabilities was similar to that seen during the last year of observation.

DS is associated with high epilepsy-related premature mortality, often attributed to SE or SUDEP, and a marked young age at death [8]. In a mostly adult population, this study reported a mortality rate of 11.88% over 10 years for patients with probable DS, significantly higher than matched controls (1.19%). Four deaths were recorded in patients aged <40 years, suggesting that DS affects life expectancy. Overall, the mortality rate falls within the range of published data in patients with DS (3.7–20.8%) [5–7]. Variability in published mortality data could result from differences in patient selection criteria, or study methodology and reporting. It is clear, however, that DS carries a significant risk of early mortality.

Interpretation of this analysis should take into account the small number of patients with probable DS that were identified, although this is unsurprising since DS is a rare condition. Our selection algorithm was informed by the methodology of previous studies in DS and other encephalopathies [15,41–43], but it is possible that misclassification of patients may have occurred. Specificity of the patient selection algorithm relies on the assumption that stiripentol and potassium bromide are rarely used in patients who do not have a diagnosis of DS. This assumption is supported by a questionnaire study conducted in Germany in which caregivers did not report any use of stiripentol or potassium bromide in children and adolescents with epilepsy over a 3-month period [44]. Although valproate and clobazam are more commonly used in patients with epilepsy, we included additional criteria (no sodium channel blockers, abnormal brain development, or competing etiologies) to further refine the identification of patients based on this criterion. While the study population may have included some patients without DS, such patients are likely to represent DEEs with a refractory course. As abnormal brain development and competing etiologies such as TSC or probable LGS were excluded by definition, this study population represents DS and similar DEEs. In addition, analyses based on healthcare insurance data may be subject to inaccuracies due to under- or over-reporting. 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 that they were captured within. Further research is necessary to validate the outcomes of this study and to determine whether the findings apply to patients with DS across Europe and the rest of the world.

5. Conclusions

In conclusion, this study adds to the limited available prevalence and healthcare resource utilization data for DS, a rare epileptic syndrome. Annual healthcare costs incurred by patients with probable DS were substantial and were mostly attributed to inpatient care, medication, and services and devices. Patients prescribed with rescue medication incurred significantly greater costs than those who were not. Probable DS was associated with a significant risk of early mortality.

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Author contributions

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

Data-sharing statement

Data were obtained by Vilua from the health insurance companies and may not be published by or shared with other institutions. Ethical approval from patients was not obtained because the data were fully anonymized and pseudonymized by the health insurance companies before transferring to Vilua.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SSB reports personal fees from UCB, Eisai, Desitin Pharma, Zogenix, and GW Pharmaceuticals companies. LK reports support for attending meetings and/or travel from Eisai and UCB Pharma. ASi is an employee of Vilua Healthcare GmbH. GW and RH are employees of GW Pharma Ltd. FR reports personal fees from Arvelle Therapeutics, Eisai, and GW Pharmaceuticals companies; personal fees and travel expenses from UCB; and grants from the Detlev-Wrobel Fonds for Epilepsy Research, BMBF – ERA PerMed Programme, Hessisches Ministerium für Wissenschaft und Kunst (LOEWE-Programme), and the European Union. ASt reports personal fees and grants from Arvelle Therapeutics, Desitin Arzneimittel, Eisai, GW Pharmaceuticals companies, Marinus Pharma, Medtronic, UCB, and Zogenix.

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Appendix A. Supplementary data

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