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Epidemiology, healthcare resource use, and mortality in patients with tuberous sclerosis complex: A population-based study on German health insurance data

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ABSTRACT

Purpose: 10-year retrospective study to assess burden of illness in individuals with tuberous sclerosis complex (TSC) identified from German healthcare data.
Methods: Patients with TSC were identified by International Classification of Diseases code Q85.1. Patients with epilepsy were identified by epilepsy diagnosis or antiseizure medication (ASM) prescription after TSC diagnosis.
Results: Using data from 2016 (final study year), 100 patients with TSC were identified (mean [range] age: 38 [1–86] years; male: 40%); prevalence: 7.9 per 100,000 (TSC), 2.2 per 100,000 (TSC with epilepsy). During the 10-year study period (2007–2016), 256 patients with TSC were identified and followed up for 1,784 patient-years (epilepsy: 36%, 616 patient-years). TSC manifestations/comorbidities (apart from epilepsy) were identified more frequently in patients with epilepsy than without. Mean annual healthcare costs for patients with TSC were €6,139 per patient-year (PPY), mostly attributable to medication (35%) and inpatient care (29%). Patients with epilepsy incurred costs more than double those without. Mean (standard deviation [SD]) annual hospitalisation rate (AHR) and length of stay (LOS) PPY: 0.5 (1.0) and 5.9 (18.6) days for TSC. AHR and LOS were greater in patients with epilepsy than without. Mean (SD) number of ASMs prescribed (TSC with epilepsy): 3.0 (2.3) over the entire observable time per patient. Mortality rates (vs. control): 5.08% (vs. 1.69%, $p<0.001$) for TSC, 7.53% (vs. 0.98%, $p<0.001$) for TSC with epilepsy, 3.68% (vs. 2.03%, $p = 0.003$) for TSC without epilepsy.
Conclusion: Healthcare costs, resource utilisation, and mortality were greater in patients with TSC and epilepsy than those without epilepsy.

1. Introduction

Tuberous sclerosis complex (TSC) is a rare, multisystem genetic disorder, characterised by the formation of tumours in various organs, such as the brain, kidneys and skin [1,2]. The disorder is highly heterogenous and is associated with a spectrum of additional neurological or neuropsychiatric manifestations including epilepsy, intellectual disability, behavioural disorders, and autism [2–4]. Epilepsy is the most

Abbreviations: AHR, annual hospitalisation rate; ASM, antiseizure medication; ATC, Anatomical Therapeutic Chemical Classification System; CI, confidence interval; CPRD, Clinical Practice Research Datalink; GKV, Gesetzliche Krankenversicherung (statutory health insurance); ICD-10, International Classification of Diseases, 10th revision; LGS, Lennox-Gastaut syndrome; LOS, length of stay; mTOR, mechanistic target of rapamycin; PPY, per patient-year; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SUDEP, Sudden Unexpected Death in Epilepsy; TOSCA, TuberOus SClerosis Registry; TSC, tuberous sclerosis complex.

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common neurological disorder in individuals with TSC and results in significant morbidity and mortality [3,5,6]. Epilepsy typically develops within the first year of life in individuals with TSC, although adults with TSC and no history of seizures remain at increased risk of epilepsy throughout their lifetime [1,3,6]. In an international registry of 2216 individuals with TSC from 31 countries, epilepsy was present in 84%, with most diagnosed at or before the age of 2 years [6]. The treatment of epilepsy in individuals with TSC may involve antiseizure medication (ASM), surgery and/or the ketogenic diet [1]. Vigabatrin is considered to be a first-line treatment option for TSC-associated seizures in the first years of life and ASM combination therapy may be initiated where monotherapy has failed [1]. Mechanistic target of rapamycin (mTOR) inhibitors, such as everolimus, have been approved to treat several manifestations of TSC, including refractory seizures [7]. Despite the range of available treatments, seizures tend to persist in around two-thirds of individuals with TSC and epilepsy [3].

While TSC is mainly diagnosed during childhood, the complexity of the disorder and its diverse manifestations throughout an individual's lifetime mean that they often require lifelong multidisciplinary care and monitoring [8]. Individuals with TSC and their families or caregivers commonly report cognitive concerns, depression, anxiety, sleep difficulties, and aggression in affected individuals [9]. Besides the impact on the individual, providing constant and long-lasting care presents a considerable responsibility for relatives and other caregivers. Accordingly, TSC may result in lifelong financial challenges and impaired work productivity for individuals and their families and caregivers [10].

Individuals with TSC and their caregivers have a high burden of illness, on average, and the condition also incurs substantial costs [11]. Despite the frequent occurrence of epilepsy with TSC, few studies have focused specifically on burden of illness in this population, suggesting a need for further data. Two of the available studies have reported direct healthcare costs related to TSC and epilepsy in the USA [12] and UK [13], while several other studies have assessed healthcare resource utilisation and/or medication use [6,14–16].

The objective of this retrospective German healthcare claims database analysis was to examine epidemiology, TSC manifestations and comorbidities, healthcare costs and resource utilisation, medication use, injuries, and mortality for individuals with TSC, including those with epilepsy.

2. Methods

2.1. Data source

This study used de-identified healthcare insurance claims data obtained from the Vilua Healthcare research database, which contains entries for >4 million individuals and represents approximately 5% of the German population covered by statutory health insurance ('Gesetzliche Krankenversicherung'; GKV). Comparison with the annual publications of the German Federal Office for Social Security ('Bundesamt für Soziale Sicherung') is conducted to ensure that the database is representative of the German population. The database has been used for previous epidemiological studies in epilepsy, status epilepticus, and probable Lennox-Gastaut syndrome (LGS) [17–20]. Data entries are routinely inspected for outliers, data errors, and longitudinal changes.

This analysis was approved by the ethics committee of the University of Frankfurt, Germany. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [21].

2.2. Patient identification

Patients with TSC were identified using the International Classification of Diseases, 10th revision (ICD-10) code Q85.1 (Fig. 1). Amongst the TSC population, patients with epilepsy were identified as those with an epilepsy claim, defined as ≥1 G40*/G41* ICD-10 code or ≥1 ASM prescription (Anatomical Therapeutic Chemical Classification System [ATC] code N03A), after TSC diagnosis.

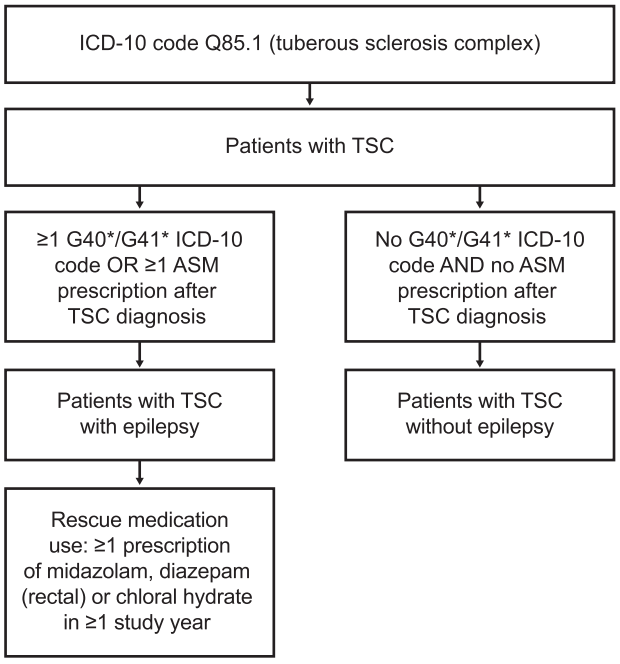

Fig. 1. Patient identification.
ASM, antiseizure medication; ICD-10, International Classification of Disease, 10th revision; TSC, tuberous sclerosis complex.

2.3. Outcomes

Data were assessed over a 10-year period between 1 January 2007 and 31 December 2016. The primary analyses were prevalence, and age and sex distribution based on the number of patients identified in the final year of the study (2016). The final year was chosen to ensure reporting of the most accurate and recent epidemiological data. Secondary analyses were annual healthcare costs, annual hospitalisation rate (AHR) and length of stay (LOS, measured in days), TSC manifestations, comorbidities, medication use, injuries, and mortality. Secondary analyses were assessed using the number of patients identified across the entire study. 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 TSC was assessed using a top-down approach, from the perspective of the statutory health insurer. This approach was applied to all hospitalisation admissions within the specified analysis period. All costs were calculated in Euro (€) and were adjusted to the 2015 price year using the German Health Consumer Price Index [22]. All patient-years were considered for the analyses regardless of incurred costs, for example for patients with no hospital admittances and costs over a year, annual cost was recorded as €0. AHR and LOS were presented for all patients and those hospitalised because of TSC. LOS at discharge was calculated.

Incidences of other TSC manifestations (during the 10-year study period) and comorbidities (during the last year) were evaluated using predefined categories based on ICD-10 codes. The number of different medications was determined from the number of different ATC codes noted throughout the study for a particular patient. The most commonly prescribed ASMs (ATC code N03A + clobazam N05BA09) were assessed using the data for each patient in their last observation year; this was either the final year of the study or the year in which the patient left the database (for example, the patient may have switched to another insurance company, left the country, or died). Incidence of injuries and mortality rate were compared with age- and sex-matched control groups

without TSC or probable LGS or Dravet syndrome. To generate these controls, 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 the patient with TSC.

2.4. Statistical analysis

All data were analysed with SQL Server 2016 SP2, R 3.6.2 and Microsoft Excel. Log rank tests using chi-squared distribution were performed to assess the significance of mortality data versus standardised controls.

Annual healthcare costs, AHR, and LOS were evaluated in a subgroup of patients with epilepsy who had been prescribed rescue medication during ≥1 study year. For this analysis, rescue medication was defined as ≥1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate.

3. Results

3.1. Prevalence

Using data from the final year of this 10-year study (2016), 100 patients with TSC were identified resulting in a prevalence (standardised to German GKV population) of 7.9 per 100,000 people. Within this TSC patient cohort, 29% were identified to have epilepsy with a standardised prevalence of 2.2 per 100,000 people.

During the 10-year study period, 256 patients with TSC were identified and followed up for 1784 patient-years. At least 1 epilepsy claim was made for 93/256 (36%) patients with 616 patient-years of follow-up. Based on age in first observation year, epilepsy was more common in children aged <14 years (35/64, 55%) and adolescents aged 14–17 years (7/12, 58%) than adults (51/180, 28%).

3.2. Patient demographics and characteristics

In the 2016 population, patients with TSC had a mean (range) age of 38 (1–86) years and 40% were male (Table 1). Over the entire study duration, other TSC manifestations apart from epilepsy were identified more frequently in patients with epilepsy than in those without (Table 1). During the last available year for each patient, those with epilepsy also had greater incidences of certain comorbidities than those without, in particular, cognitive disabilities and incontinence (Fig. 2).

Table 1
Demographics and TSC manifestations, apart from epilepsy, in patients with TSC.

	Patients with TSC		
	All patients	With epilepsy[a]	Without epilepsy
Patients identified in 2016			
Number of patients (%)	100	29 (29)	71 (71)
Mean age, years (range)	38 (1–86)	28 (2–86)	42 (1–79)
Sex, male, n (%)	40 (40)	10 (34)	30 (42)
Patients identified during the 10-year study period			
Number of patients (%)	256	93 (36)	163 (64)
TSC manifestations*[b], *n (%)			
Lung	44 (17)	22 (24)	22 (13)
Renal	74 (29)	34 (37)	40 (25)
Psychotic and affective disorders	203 (79)	82 (88)	121 (74)
Developmental and cognitive disorders	46 (18)	34 (37)	12 (7)

ASM, antiseizure medication; ICD-10, International Classification of Diseases, 10th revision; TSC, tuberous sclerosis complex.

[a] Epilepsy defined as ICD-10 code G40* or G41* or ≥1 ASM prescription after TSC diagnosis.

[b] Lung defined as ICD-10 code J80*–J84* or J98*; renal defined as ICD-10 code N10*–N19*, I12*–I13*, N28.1, C64*, D17*, or D30*; psychotic and affective disorders defined as ICD-10 code F06*–F07*, F09*, F20*–F29*, F30*–F39*, F40*–F48*, F60*–F69*, F70*–F79*, F80*–F89* or F90*–F98*; developmental and cognitive disorders defined as ICD-10 code F71*–F78*, F84*, or F98*.

3.3. Annual healthcare costs

3.3.1. All patients

During the 10-year study period, the mean annual cost of healthcare was €6139 per patient-year (PPY; Table 2). Healthcare costs were mostly attributable to medication (35%) and inpatient care (29%).

3.3.2. Patients with epilepsy

Patients with epilepsy incurred more than twice the mean annual healthcare costs of those without epilepsy (€9091 vs. €4583 PPY; Table 2). In particular, patients with epilepsy had greater medication costs (€3819 vs. €1261 PPY), although only a small proportion of this cost (12%) was attributed to ASMs. Everolimus was the most expensive non-ASM, prescribed to 4 patients with epilepsy (4.3%; total of 68 prescriptions at a mean cost of €6205 per prescription) and 2 patients without epilepsy (1.2%; 30 prescriptions, €5238). The substantial non-ASM cost was influenced by prescription of several other high-cost medications (>€1000 mean cost per prescription), including temozolomide (ATC code L01A), interferon beta 1-alpha (L03A), sirolimus (L04A), and magnetic resonance imaging contrast media (V08C). Inpatient costs were also greater in patients with epilepsy than those without (€2356 vs. €1517 PPY); this difference was more evident when considering hospital admissions related to TSC (€1263 vs. €146 PPY).

3.4. Annual hospitalisation rate and length of stay

3.4.1. All patients

In the overall TSC population, mean (standard deviation [SD]) AHR and LOS were 0.5 (1.0) PPY and 5.9 (18.6) days PPY during the 10-year study period; both parameters had a wide range (Table 3). The most common reasons for hospitalisation (primary or secondary diagnosis) were TSC as part of the ICD-10 code Q85* for phakomatoses (22%) and epilepsy and recurrent seizures (22%, G40*).

3.4.2. Patients with epilepsy

During the 10-year study period, the mean hospitalisation rate in patients with epilepsy was almost double that of those without epilepsy (0.7 vs. 0.4 per patient-year; Table 3) and mean LOS was numerically longer (8.4 vs. 4.6 days). The most common reasons for hospitalisation (primary or secondary diagnosis) were epilepsy and recurrent seizures (63%, ICD-10 code G40*) and phakomatoses including TSC (41%, Q85*). In addition, 8% of patients were hospitalised due to status epilepticus (G41*).

3.5. Medication use

3.5.1. All patients

During the 10-year study period, the mean (SD; median) number of different medications prescribed was 6.3 (5.1; 5) PPY and 19.2 (14.4; 15) over the entire observable time for each patient. The most commonly prescribed medications (≥10%) were ibuprofen (425 patient-years, 24%), levothyroxine (203 patient-years, 11%) and metamizole (181 patient-years, 10%).

3.5.2. Patients with epilepsy

During the 10-year study period, patients with epilepsy were prescribed a mean (SD; median) of 7.7 (5.6; 6) different medications PPY and 21.6 (16.9; 17) over the entire observable time. ASMs accounted for a mean (SD; range) of 2.0 (1.1; 1–7) of the medications prescribed PPY and 3.0 (2.3; 1–11) over the entire observable time. Patients were typically prescribed one (32%), two (18%) or three (10%) ASMs during the study duration. For patients with epilepsy who had ≥1 ASM

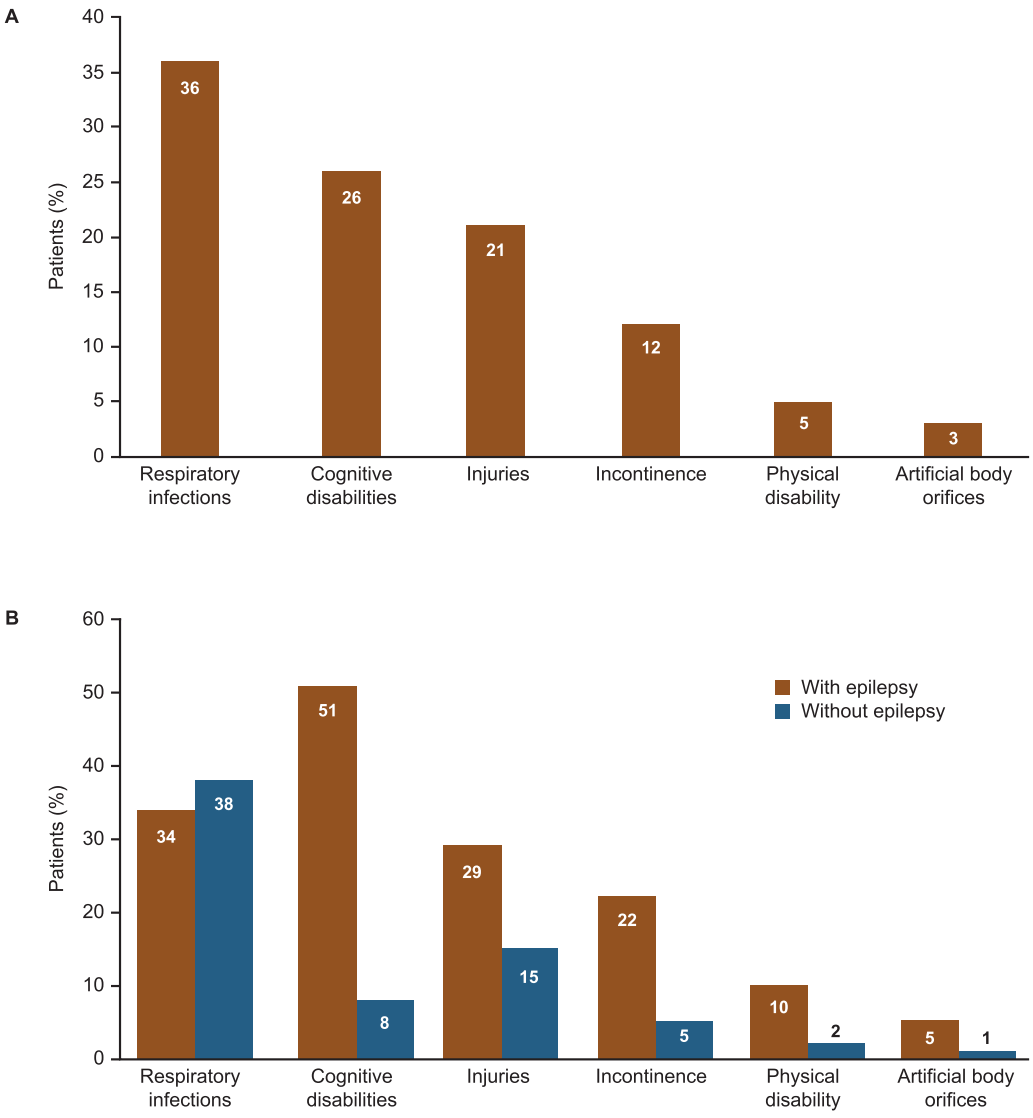

Fig. 2. Comorbidities during the last year for all TSC patients (A) and patients with and without epilepsy (B).
TSC, tuberous sclerosis complex.

prescription during the last study year (n = 60), the most commonly prescribed ASMs or combinations of ASMs (≥10%) were carbamazepine (11 patients, 18%), lamotrigine and valproate (11 patients, 18%), and oxcarbazepine (10 patients, 17%; Supplementary Table 1). The most commonly prescribed ASMs over the study duration (≥10%) were valproate (141 patient-years, 23%), lamotrigine (116 patient-years, 19%), carbamazepine (101 patient-years, 16%), oxcarbazepine (98 patient-years, 16%), vigabatrin (77 patient-years, 13%), and levetiracetam (71 patient-years, 12%).

3.6. Rescue medication use

Rescue medication was prescribed on ≥1 occasion for 28/93 (30%) of the patients with epilepsy, providing 89/616 (14%) patient-years for analysis. Mean (SD) annual total cost of healthcare was €20,793 PPY. Main contributors to healthcare costs were medication (€10,879, 52%), inpatient care (€4931, 24%), services and devices (€3296, 16%), and outpatient care (€1687, 8%). ASMs made up a small proportion of the medication costs (€823/€10,879, 8%). In patients who were prescribed rescue medication, mean (SD) AHR and LOS were 1.7 (1.8) PPY and 18.6 (34.2) days PPY.

3.7. Injuries

Injuries were numerically more common in patients with epilepsy compared with control (67% vs. 54%), largely due to a greater incidence of head injuries (29% vs. 17%) and trunk injuries (42% vs. 35%).

3.8. Mortality

Over the 10-year study period, the mortality rate for patients with TSC was significantly higher than that observed in the control group: 5.08% (13 deaths) vs. 1.69% (398 deaths), $p<0.001$ (Fig. 3A). One patient died at the age of 8 years; the remaining 12 were aged between 56 and 96 years (mean 77 years).

Seven of the 13 deaths in patients with TSC occurred in those patients with epilepsy resulting in a significantly greater mortality rate than control: 7.53% (7 deaths) vs. 0.98% (89 deaths), $p<0.001$; Fig. 3B). Mortality rate in patients without epilepsy was 3.68% (6 deaths) vs. control 2.03% (309 deaths), $p = 0.003$.

4. Discussion

This retrospective study presents analyses of prevalence, healthcare

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

	Patients with TSC All patients		Patients with epilepsy[a]		Patients without epilepsy	
Patient-years	1784		616		1168	
Annual cost per patient-year, €						
	Mean	**Median (Q1–Q3)**	**Mean**	**Median (Q1–Q3)**	**Mean**	**Median (Q1–Q3)**
Total	6139	853 (0–4415)	9091	2221 (0–7053)	4583	560 (0–2859)
Inpatient	1807	0 (0–124)	2356	0 (0–1246)	1517	0 (0–0)
TSC-related [%[b]]	528 [29]	0 (0–0)	1263 [54]	0 (0–51)	146 [10]	0 (0–0)
Outpatient	749	245 (0–865)	1053	291 (0–957)	589	225 (0–823)
Medication	2144	77 (0–772)	3819	449 (0–2225)	1261	42 (0–320)
ASMs [%[c]]	161 [8]	0 (0–0)	465 [12]	5 (0–416)	0	0 (0–0)
Services and devices	942	0 (0–452)	1480	46 (0–1571)	658	0 (0–248)
Special equipment	121	0 (0–0)	203	0 (0–0)	78	0 (0–0)
Other physical therapies	37	0 (0–0)	77	0 (0–0)	15	0 (0–0)
Home nursing care	31	0 (0–0)	19	0 (0–0)	38	0 (0–0)
Physiotherapy	25	0 (0–0)	36	0 (0–0)	19	0 (0–0)
Transport for medical needs	24	0 (0–0)	48	0 (0–0)	11	0 (0–0)
Other costs	704	0 (0–279)	1097	0 (0–938)	496	0 (0–151)
Dialysis	230	0 (0–0)	325	0 (0–0)	179	0 (0–0)
Sick pay	268	0 (0–0)	58	0 (0–0)	379	0 (0–0)

ASM, antiseizure medication; ICD-10, International Classification of Diseases, 10th revision; Q1–Q3, interquartile range; TSC, tuberous sclerosis complex.
[a] Epilepsy defined as ≥1 G40*/G41* ICD-10 code or ≥1 ASM prescription after TSC diagnosis.
[b] Percentage of mean total inpatient cost.
[c] Percentage of mean total medication cost.

Table 3
Annual hospitalisation rate and length of stay for patients with TSC during the 10-year study period.

	Patients with TSC All patients		Patients with epilepsy[a]		Patients without epilepsy	
Patient-years	1784		616		1168	
	AHR, PPY	**LOS, days PPY**	**AHR, PPY**	**LOS, days PPY**	**AHR, PPY**	**LOS, days PPY**
All patients						
Mean (SD)	0.5 (1.0)	5.9 (18.6)	0.7 (1.2)	8.4 (21.4)	0.4 (0.8)	4.6 (16.8)
Median	0	0	0	0	0	0
Range	0–9	0–264	0–8	0–183	0–9	0–264
95% CI	0.4–0.5	5.0–6.8	0.6–0.8	6.7–10.1	0.3–0.4	3.6–5.5
Patients hospitalised because of TSC						
Mean (SD)	0.2 (0.6)	1.6 (10.0)	0.4 (1.0)	4.3 (16.3)	0.01 (0.1)	0.2 (2.7)
Median	0	0	0	0	0	0
Range	0–7	0–183	0–7	0–183	0–3	0–57
95% CI	0.1–0.2	1.2–2.1	0.4–0.5	3.1–5.6	0–0.02	0.1–0.4

AHR, annual hospitalisation rate; ASM, antiseizure medication; CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision; LOS, length of stay; PPY, per person-year; SD, standard deviation; TSC, tuberous sclerosis complex.
[a] Epilepsy defined as ≥1 G40*/G41* ICD-10 code or ≥1 ASM prescription after TSC diagnosis.

costs, hospitalisations, medication use, and mortality in individuals with TSC in Germany over a 10-year period. This study adds relevant data about the economic burden of TSC within Europe and offers insight into the treatment needs of individuals with TSC and epilepsy.

Using data from the final year of our study, 100 patients with TSC were identified giving a standardised prevalence of 7.9 per 100,000 people. These data are in keeping with previous analyses, which have reported a prevalence of TSC ranging from 2.9 to 8.8 per 100,000 [15,23,24]. As noted previously, TSC is highly variable in its clinical presentation and symptoms can develop and change throughout life. Since milder cases may potentially go undetected, the incidence of TSC may be underestimated [25].

Epilepsy was identified in 36% of patients with TSC during the 10-year study period; this proportion is much lower than has been previously reported (63–93%) [3,5,6,13,15,26–29]. This discrepancy may be explained, at least in part, by our general population-based patient selection in contrast with studies based on populations attending specialist TSC or epilepsy centres. It has been suggested that non-population based studies may overestimate the prevalence of epilepsy [15]. In our analysis, epilepsy was identified by the broad definition of either an ICD-10 code for epilepsy or ≥1 ASM prescription after TSC diagnosis. Under-reporting or underdiagnosis of epilepsy and the observation that some individuals with TSC and epilepsy are not treated with ASMs [13] may also have contributed to the findings. In our analysis, patients without epilepsy had a lower incidence of other TSC-related manifestations and some comorbidities than those with epilepsy. It is possible that, due to increased familial genetic screening in Germany, the clinical profile of TSC amongst the general population has changed to include more individuals with asymptomatic or milder forms of the condition. It should also be noted that the study population was largely adult with 73% aged ≥20 years, and epilepsy was less commonly reported in adults than children and adolescents. Epilepsy associated with TSC most often develops in infancy or early childhood, although patients remain at risk of epilepsy throughout their lifetime [6].

Rescue medication was only prescribed to 30% of the patients with TSC with epilepsy in this study. This finding is in line with other studies that have also shown that most patients with epilepsy are not prescribed rescue medication. For example, 27.9% of adults with epilepsy who attended an epilepsy outpatient clinic in Germany reported that they had been prescribed emergency medication during the past year [30].

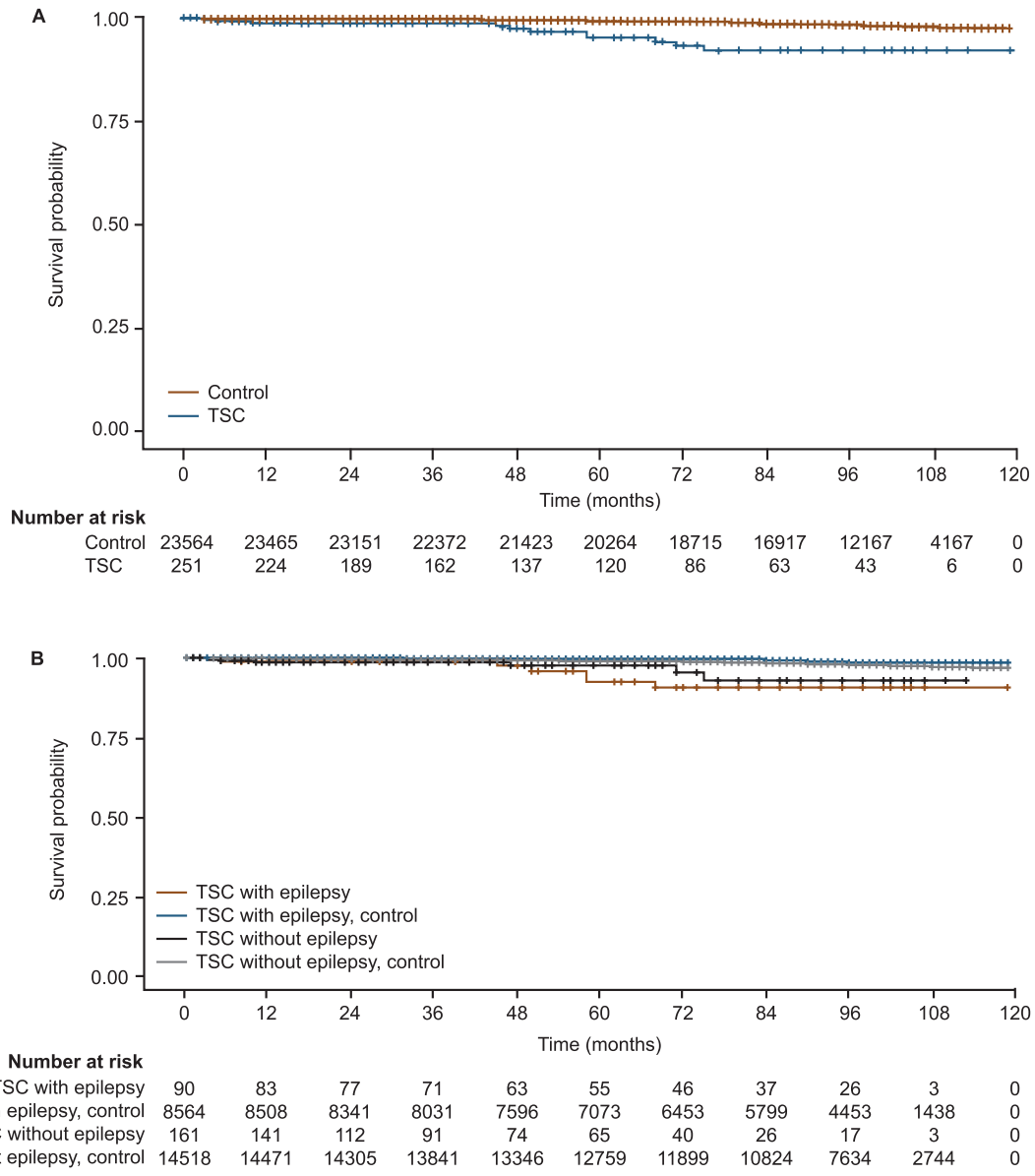

Fig. 3. Survival rate of patients with TSC (A) and patients with TSC with and without epilepsy (B) vs. control groups[a] during the 10-year study period. TSC, tuberous sclerosis complex. [a]The control group consists of individuals of the same age and sex distribution over an equal observation time.

Another German healthcare insurance database analysis of patients with probable LGS reported rescue medication prescription during 45% of patient-years over a 10-year period [20].

Patients with TSC incurred substantial mean total healthcare costs of €6139 PPY. Medication comprised the greatest component of the total costs (35%); this was strongly influenced, however, by some expensive drugs that were prescribed to a few patients. Further, patients with TSC and epilepsy had greater healthcare costs than those without epilepsy (€9091 vs. €4583 PPY). Patients with epilepsy who were prescribed rescue medication had particularly high costs (€20,793 PPY), although interpretation of this finding should take into account the low proportion of patient-years with prescribed rescue medication (14%). Overall, these findings are consistent with previous studies that have reported that individuals with TSC incur higher healthcare costs than the general population due to the chronic and multisystem nature of the condition [11]. For example, long-term data from the UK Clinical Practice Research Datalink (CPRD) reported costs for TSC that were almost triple those of the control population [31]. A recent 3-month retrospective questionnaire study revealed substantial direct and indirect healthcare costs associated with TSC in Germany [32]. Two previous studies have reported high healthcare costs specifically for individuals with TSC and epilepsy, although neither analysis compared costs for those with and without epilepsy [12,13]. Authors of a study based on the UK CPRD concluded that the high costs incurred by individuals with TSC and epilepsy are likely to reflect the diverse and severe TSC-related manifestation profile of the individuals, since having 2 or more TSC manifestations was found to be a significant cost driver [13]. Data from US health insurance claims databases showed that individuals with TSC and epilepsy who had a medically-treated seizure event had substantial annual all-cause healthcare costs [12]. Higher medical costs for maintenance care in individuals who had a medically-treated seizure compared with those who did not were attributed to the increased costs of care associated with severe drug-resistant epilepsy syndromes [12]. Taken together, these findings highlight the economic impact of drug-resistant seizures in this population.

Inpatient care was the second highest component of the annual healthcare costs for patients with TSC and this was reflected in the mean AHR (0.5 PPY) and LOS (5.9 days PPY). Previous research has found that

hospitalisation rates in individuals with TSC are at least twice as high as those in the general population [11]. Our findings highlighted the increased AHR and longer LOS in patients with TSC and epilepsy (mean 0.7 and 8.4 days PPY). A study based in the UK reported that individuals with TSC and epilepsy had almost triple the number of inpatient admissions over 3 years than matched controls, although LOS was similar between the 2 populations [13]. In the US, amongst patients with TSC and epilepsy, inpatient admissions were greater in those with at least 1 medically-treated seizure event than those without (0.5 vs. 0.1–0.2 PPY) [12].

Patients with TSC and epilepsy were generally prescribed between 1 and 3 ASMs over the study duration, most commonly valproate (23%), lamotrigine (19%), carbamazepine (16%), and oxcarbazepine (16%). Likewise, other studies based in Europe have reported that individuals with TSC and epilepsy are typically prescribed between 1 and 3 ASMs [13,20,33]. Similar to our findings, the most frequently prescribed ASMs in Sweden to individuals with TSC-associated epilepsy were valproate (45%), lamotrigine (43%), carbamazepine (38%), levetiracetam (37%), and topiramate (24%) [15]. The TuberOus SClerosis Registry (TOSCA) reported that almost all individuals with TSC and focal seizures (98.1%) and/or infantile spasms (96.7%) received treatment, most often with vigabatrin [6]. Vigabatrin is recommended as first-line treatment for infantile spasms with TSC and focal seizures below the age of 1 year [1, 8]; this may explain the lack of vigabatrin use in our study where all patients with epilepsy were aged ≥2 years. Over the last 10 years, everolimus has been sequentially approved in Europe for the treatment of TSC-related subependymal giant cell astrocytomas, angiomyolipomas, and treatment-refractory epilepsy. A recent retrospective chart review showed that everolimus is effective as an add-on treatment in adult patients with TSC and epilepsy, without an upper age limit for individual benefit [34]. Although everolimus has been available in Germany for many years as a treatment for TSC, EU approval for treatment-refractory epilepsy was not obtained until after the end of our study, which may contribute to the low use of everolimus in patients with TSC with epilepsy. Nevertheless, other studies have also reported that mTOR inhibitors (everolimus, sirolimus) are used infrequently (5.5–15.3% of patients) in this population [6,15,16].

Despite the availability of several treatment options for patients with TSC and epilepsy, including medication, surgery, and ketogenic diet, up to 75% of patients develop refractory epilepsy [35,36]. New effective ASMs with different modes of action would be welcome advances for this patient population. A recent update to the use of everolimus may provide an additional treatment option for patients with TSC and epilepsy. In addition, highly purified cannabidiol (CBD) has been approved for the treatment of seizures associated with TSC in patients ≥1 years of age in the USA (Epidiolex®, Greenwich Biosciences, Inc.) and, more recently, for the adjunctive treatment of seizures associated with TSC in patients ≥2 years of age in the EU and Northern Ireland (Epidyolex®, GW Pharma [International] B.V.). In a double-blind randomised trial in patients with TSC and frequent, treatment-resistant seizures, add-on CBD significantly reduced seizure frequency compared with placebo [37]. Overall, CBD had an acceptable safety profile in this trial.

Patients with TSC and epilepsy reported a numerically greater incidence of head injuries versus control (29% vs. 17%, respectively). Individuals with TSC and epilepsy can present with a variety of seizure types, including atonic or drop seizures; a lack of seizure control (as is often seen with TSC and epilepsy) and a high number of atonic seizures could be the reason for this notably high incidence of head injuries [38]. The serious problem of injuries caused by seizures and the potential for better seizure control to prevent injuries have been highlighted in other studies of patients with drug-resistant epilepsy [39,40].

Consistent with previous research, mortality in individuals with TSC was significantly greater over 10 years than in the control population (5.08% vs. 1.69%, $p<0.001$), and was particularly high in individuals with TSC and epilepsy (7.53% vs. 0.98%, $p<0.001$). Other studies have reported long-term mortality rates ranging from 5% to 13.8% in individuals with TSC (excluding studies of individuals with TSC and specific complications) [41–43]. Although there is a lack of published mortality data in individuals with TSC and epilepsy, the most common cause of TSC-attributable death is related to epilepsy, including status epilepticus and Sudden Unexpected Death in Epilepsy (SUDEP), followed by kidney complications, and systemic infections [11]. In a 10-year study of Swedish healthcare data, 551 individuals with TSC, including 386 (70%) with epilepsy, were identified and 30/386 (7.8%) of those with TSC and epilepsy died [15]. The cause of death was directly related to TSC in 15 (50%) cases. These data underline the high mortality risk in individuals with TSC, particularly in those with drug-refractory epilepsy.

Limitations of this analysis include potential coding inaccuracies within the healthcare insurance database. Few patients were identified who had TSC and were aged less than 2 years, and none of these had TSC with epilepsy. Coding for diagnosis of a genetic disorder in the healthcare insurance database is often delayed while genetic testing is conducted and processed, and, in some cases, genetic testing may be deferred until a later date. As patient data reviewed within this study were obtained from a German healthcare database, further research is necessary to validate the outcomes of this study and to ensure that findings are applicable to individuals with TSC across Europe and the rest of the world.

5. Conclusion

These data provide valuable insight into the economic burden of TSC and TSC-associated epilepsy in Germany. Occurrence of epilepsy in patients with TSC was lower than expected, potentially due, at least in part, to the population-based, rather than epilepsy centre-based, patient selection. Healthcare costs, resource utilisation, and mortality were greater in patients with TSC and epilepsy than those without epilepsy.

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Data statement

Data were obtained by Vilua from the health insurance companies and may not be published by or shared with other institutions. Informed consent from patients was not obtained because the data were fully anonymised and pseudonymised by the health insurance companies before transferring to Vilua.

Author contributions

All authors contributed to conceptualisation, methodology, and writing – review and editing. ASi conducted the formal analysis.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.06.027.

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