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Epileptic Disorders

Long-term outcome of convulsive status epilepticus: a 10-year follow-up

Rosa Kling[1], Jaakko Ritvanen[1], Harri Mustonen[2], Leena Kämppi[3]

[1] Clinical Neurosciences, Neurology, University of Helsinki and Department of Neurology, Helsinki University Central Hospital, Finland
[2] Department of Surgery, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
[3] Epilepsia Helsinki, Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

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ABSTRACT

Objective. This study aimed to determine the mortality, causes of death and factors affecting the outcome of convulsive status epilepticus (CSE) at 10 years.

Method. This retrospective study consisted of 62 consecutive adult patients diagnosed with CSE at the Helsinki University Hospital (HUS) emergency department during 2002-2003. Patients were followed for up to 10 years or up to the time of death. Data on patient demographics, CSE characteristics, treatment, complications, and outcome from the time of CSE were collected. The Official Statistics of Finland provided the information on mortality and causes of death. Survival analysis was conducted using Cox proportional hazards regression analysis.

Results. In-hospital mortality was 8.1%, and mortality was 25.8% at one year, 51.6% at five years and 64.5% at 10 years. Estimated standardized mortality ratio (SMR) was 5.3 and the deceased patients lost 20.9 potential years of life, on average. The leading causes of death were disorders of the brain or the circulatory system, epilepsy-related conditions or intracranial tumours. The univariable survival analysis demonstrated that age ≥65 (HR=2.8, p=0.001), Charlson Comorbidity Index (CCI)>0 (CCI=1-3: HR=3.0, p=0.009; CCI>3: HR=8.4, p<0.001), Status Epilepticus Severity Score (STESS)>4 (HR=5.3, p<0.001) and Epidemiology-Based Mortality Score (EMSE-EAC)>15 (HR=2.2, p=0.036) were risk factors and a Glasgow outcome scale (GOS) of 5 at discharge (HR=0.14, p=0.025) was a protective factor for survival. The multivariable analysis established STESS>4 (HR=5.0, p=0.002) and CCI>0 (CCI=1-3: HR=2.9, p=0.015; CCI>3: HR=6.3, p=0.006) as independent risk factors and GOS>3 (time-dependent) (GOS=4: HR=0.33, p=0.048; GOS=5: HR=0.13, p=0.019) as a protective factor for survival.

Significance. The rate of long-term mortality and number of potential years of life lost were high. Factors demonstrative of the overall situation of the patients, such as comorbidities, functional state after CSE and age, were significant predictors for long-term outcome.

Key words: mortality, STESS, EMSE, cause of death, comorbidity

Status epilepticus (SE) is a life-threatening neurological emergency that calls for immediate care. Currently, convulsive status epilepticus (CSE) is defined as an abnormally prolonged seizure lasting at least five minutes, or consecutive seizures without return of consciousness. After 30 minutes, there is a significant risk of neuronal injury [1]. The old definition used the 30-minute mark as the definitive time point [2]. Incidence of SE ranges from 10 to 41 per 100,000 [3]. Reported short-term mortality up to 30 days after hospitalization ranges between 7.6% and 22% [4], and long-term mortality from one year to 10 years is reported at 17-43% [5-7] using the old definition of

• **Correspondence:**
Rosa Kling Clinical Neurosciences, Neurology, University of Helsinki and Department of Neurology, Helsinki University Central Hospital, Finland
<rosa.kling@helsinki.fi>

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▼ **Table 1.** Comparison of studies on long-term mortality of status epilepticus (SE).

Study	SE definition used	Follow-up period	Mortality
Logroscino *et al.* [7]	old definition	10 y	43%*
Logroscino *et al.* [6]	old definition	10 y	31%
Tiamkao *et al.* [5]	old definition	10 y	17%
Ristic *et al.* [13]	old definition	12 y (median)	22%*
Rodin *et al.* [8]	current definition	3 y (median)	54%
Aukland *et al.* [10]	current definition	2 y (median)	42%
Møller *et al.* [9]	current definition	2 y (median)	56%

Old definition: seizure lasting ≥30 minutes; current definition: seizure lasting ≥5 minutes.
*30-day survivors.

CSE and 42-56% using the current definition [8-10]. A comparison of studies on long-term mortality is presented in *table 1*.

Although SE is known to be associated with high long-term mortality, the data is scarce and the indisputable determinants of mortality still remain relatively unclear. Many studies on long-term mortality reported a maximum follow-up period of just over three years [8, 10-12], while a few reported follow-up as long as 10 years [5-7,13]. This complicates the comparison of results. Factors associated with long-term mortality based on prior studies include progressive and acute symptomatic aetiologies, comorbidities, complications during treatment, functional outcome at hospital discharge, age and seizure duration [5, 7, 13, 14]. Also, the Status Epilepticus Severity Score (STESS) [15] and Epidemiology-based Mortality Score of SE (EMSE) [16] have been shown to predict long-term outcome [9-12]. Studies on short-term mortality after SE show mainly the same factors [12, 17-20]. However, a prior study, based on some of the patients of the present cohort, compared factors associated with mortality at 90 days and at one year after SE and showed that some predictive factors change over time, especially regarding delays in treatment [14]. This raises the question of how the predictive factors may alter further as more time passes.

The research on long-term mortality regarding causes of death and potential years of life lost (PYLL) in SE patients is scarce. Few studies have addressed the causes of death, reporting both the underlying cause of SE and comorbidities as common causes of death [6, 13, 21, 22].

This study examines the outcome of CSE patients at 10 years. The purpose was to define mortality and analyse the causes of death. Furthermore, the intention was to analyse whether CSE itself has an independent effect on mortality after 10 years or an impact on life expectancy in these patients.

Materials and methods

Study design and setting

This was a retrospective cohort study of CSE patients with a 10-year follow-up from Helsinki University Hospital (HUS). The original cohort was established in 2002-2003.

HUS is the largest tertiary care hospital in Finland providing a neurological emergency service 24/7 directly to 1.7 million inhabitants in the hospital district. Other emergency departments (EDs) in the district are located in regional hospitals and run by internists. The local emergency medical service (EMS) transports patients, independent of the impact of CSE on daily living, primarily to HUS. Additionally, patients with the most severe forms of SE, *e.g.* super-refractory SE (SRSE), are referred to HUS from a larger catchment area of 2.2 million inhabitants.

This study conforms to Finnish legislation concerning medical research, and permission was obtained from HUS and the Official Statistics of Finland. Due to the retrospective nature of the study, no ethical approval or patient consent was needed. This manuscript adheres to the applicable Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

SE definitions

At the time of data collection, CSE was defined as a continuous seizure lasting for at least 30 minutes or as multiple consecutive seizures without return of consciousness. In addition, according to the local

guidelines, the appearance of more than four seizures within an hour, irrespective of return of consciousness, was considered as SE and included in the study. Patients with convulsive seizures and impaired consciousness at any point during SE were considered as having CSE.

Selection of participants

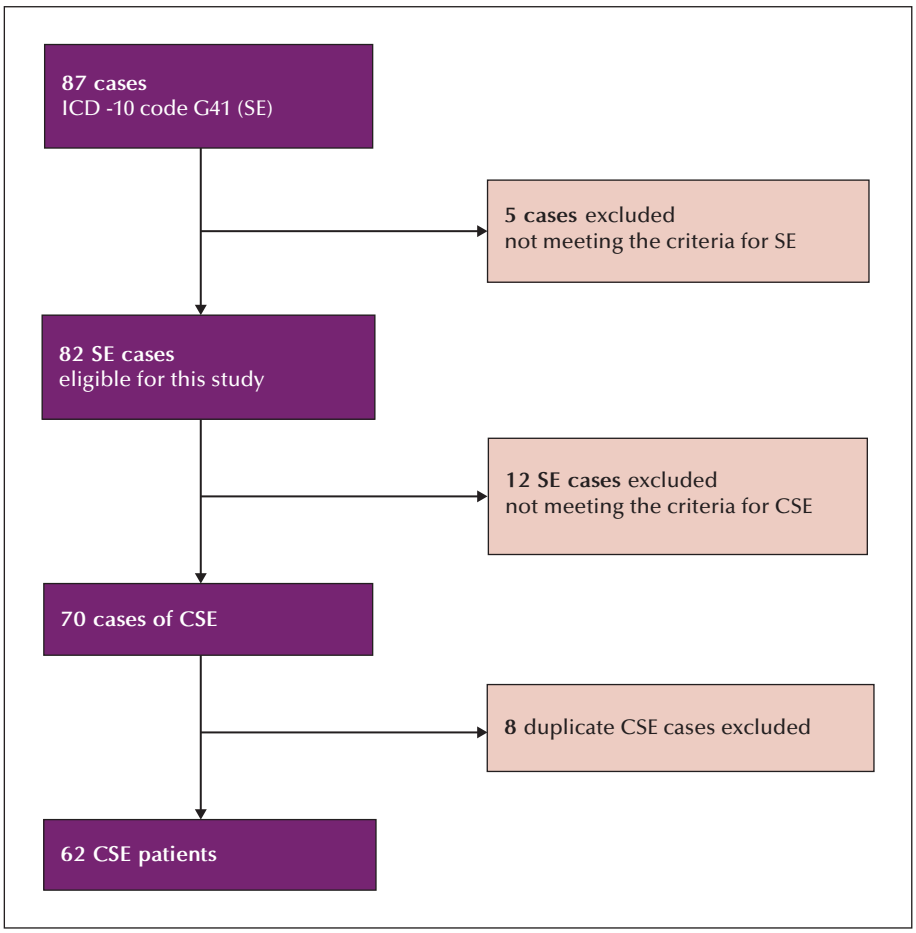
The cohort consisted of adult (≥16 years) patients who were diagnosed with CSE and treated in HUS ED between January 2002 and December 2003. Participants were identified from the HUS electronic patient database based on ICD-10 code G41 (SE). Of the 87 identified SE cases, 70 met the criteria for CSE in 62 individual patients. These 62 CSE patients were included in the study. The selection of participants is outlined in *figure 1*.

Data collection

Clinical data during the period of study of CSE was gathered from the original medical records and recorded in an electronic database. Patient identification information was removed before further analyses. Information concerning patient demographics, characteristics of CSE, treatment, complications and outcome at hospital discharge was collected.

Patients were followed from the onset of CSE up to 10 years or death. Mortality up to 10 years and causes of death were collected from the Causes of Death-register administered by the Official Statistics of Finland. The register is compliant with World Health Organisation standards.

Patient demographics, characteristics of CSE, treatment, complications and outcome are summarised in *table 2*.



■ **Figure 1.** Flowchart showing the selection of patients.

▼ **Table 2.** Summary of the patient cohort: patient demographics, characteristics of convulsive status epilepticus (CSE), treatment, complications and outcome.

Variable		*N*	%
All		62	100
Demographics and medical history			
Gender	Male	32	51.5
	Female	30	48.4
Age under 65	Yes	45	72.6
	No	17	27.4
Presence of any co-morbidity	Yes	62	100
	No	0	0
Number of co-morbidities (median/IQR)		3	1
Epilepsy	Yes	38	61.3
	No	23	37.1
	Unknown	1	1.5
Prior structural brain abnormality	Yes	35	56.5
	No	27	43.5
Charlson comorbidity index (CCI)	0	17	27.4
	1	14	22.6
	2	16	25.8
	3	10	16.1
	>3	5	8.1
Premorbid GOS	3	5	8.1
	4	32	51.5
	5	25	40.3
CSE characteristics			
Aetiology	Acute symptomatic	31	50.0
	Remote symptomatic	18	29.0
	Progressive symptomatic	5	8.1
	Unknown	8	12.9
STESS	2	29	46.8
	3	16	25.8
	4	8	12.9
	5	9	14.5
EMSE-EAC	<15	17	27.4
	15-26	18	29.0
	>26	27	43.5
Pre-status period	Yes	13	21.0
	No	49	79.0
SE onset	Continuous	40	64.5
	Intermittent	22	35.5
Refractoriness	Non-SRSE	34	54.8
	SRSE	28	45.2

▼ **Table 2.** Summary of the patient cohort: patient demographics, characteristics of convulsive status epilepticus (CSE), treatment, complications and outcome (*continued*).

Variable		*N*	%
Treatment and complications			
Anaesthesia	No anaesthesia	8	12.9
	Only propofol	48	77.4
	Multiple anaesthetics	6	9.7
Burst-suppression	Yes	25	40.3
	No	37	59.7
Complication Burden Index (CBI)	0-3	34	54.8
	>3	28	45.2
Use of vasopressors	Yes	43	69.4
	No	19	30.6
Mechanical ventilation	Yes	54	87.1
	No	8	12.9
Infections	Yes	53	85.5
	No	9	14.5
Outcome			
GOS at discharge	≤3	25	40.3
	>3	37	59.7
Condition at discharge	Worse-than-baseline	38	61.3
	Baseline	24	38.7
In-hospital mortality	Yes	5	8.1
	No	57	92
1-year mortality	Yes	16	25.8
	No	46	74.2
5-year mortality	Yes	32	51.5
	No	30	48.4
10-year mortality	Yes	40	64.5
	No	22	35.5

Outcome measures

Outcome at the end of the CSE treatment period was defined based on in-hospital mortality, condition relative to baseline, and Glasgow Outcome Scale (GOS) at hospital discharge, with GOS>3 denoting good outcome.
Long-term outcome was defined as the period up to a mortal event, occurring during follow-up.

Parameters regarding causes of death

The cause of death was considered epilepsy related when the official cause of death was epilepsy, SE or sudden unexpected death in epilepsy (SUDEP). The research group reviewed the clinical data and the death certificates to determine other factors contributing to death, in addition to the reported official cause of death. An immediate or contributing cause of death was epilepsy related when epileptic seizure or SE was an integral part of the sequel leading to death.

Parameters at the time of CSE

The classification of age as a grouping variable was set at 65 years. Patients with a prior epilepsy diagnosis were considered to have epilepsy. Comorbidity was scored according to the Charlson Comorbidity Index (CCI) [23]. CCI was used to demonstrate the overall burden of comorbidities in SE patients, and therefore also the underlying aetiologies of CSE were included. Since the CCI does not include all comorbidities, the presence of any comorbidity was also determined, as well as the presence of prior structural brain

abnormalities. The underlying aetiologies of CSE were determined according to classification of aetiologies, suggested in a report of the ILAE task force [1]. The severity of SE was scored for all patients using the STESS [15]. The EMSE mortality score was calculated, as well as the following parameters: aetiology, age and comorbidity (EMSE-EAC) [16]. EMSE-EAC considers aetiology as an individual parameter, and, consequently, the underlying aetiologies of CSE were excluded when scoring the comorbidities for EMSE. The pre-status period included seizures occurring within 48 hours prior to CSE onset. SE onset was considered continuous when the seizures lasted clinically for at least 30 minutes. Otherwise, the onset was defined as intermittent. The definition for refractory SE (RSE) was failure to respond to first- and second-stage treatment, whereas SE continuing or recurring 24 hours or more after the onset of anaesthesia was considered SRSE. Anaesthetic treatment was grouped as: no anaesthesia, only propofol or multiple anaesthetics. The Complication Burden Index (CBI) [24], as a continuous variable and with a cut-off point of >3, was used to assess complications during the treatment period.

The onset of CSE was considered as the beginning of the first seizure in accordance with the definition of CSE. The first administered antiepileptic drug, regardless of whether it was first-stage medication or not, was defined as the initial treatment. Second-stage treatment was considered as the first administered second-stage medication. Diagnosis was clinically established by the EMS or ED physician, or SE was identified based on an electroencephalogram (EEG). The tertiary hospital in this study refers to the HUS ED. Burst-suppression (BS) was defined as the beginning of the first BS sequence, clinical seizure freedom as the end of the last clinical convulsion, and return of consciousness as the point in time when the patient was no longer considered to have altered mental status. The period of time with anaesthesia and treatment in the intensive care unit was calculated by adding up the total lengths of all individual treatment periods during the CSE episode.

Statistics

Results are presented as number of cases and percentage or median and interquartile range (IQR). PYLL was calculated by subtracting the survival time of a CSE patient who died during follow-up from the life expectancy of a reference person of the same age, sex and from the same time period. This data was obtained from the database of Statistics of Finland. One patient lived longer than the reference life expectancy, therefore his PYLL was set to zero. The relative 10-year survival was estimated by dividing the 10-year survival of the patients by the 10-year survival of the above-mentioned reference population. Standardized mortality ratio (SMR) was estimated using an indirect method by dividing the observed deaths of patients by the expected deaths in the reference group from the same area and time period, separated by age (quartiles from patients) and sex. Asymptotic 95% confidence intervals (CI) were calculated for SMR and relative 10-year survival.

Survival analyses were performed using Cox proportional hazards regression analysis and the Kaplan-Meier method with the log rank test. The Cox regression assumption of constant hazard ratios over time was assessed with the Schoenfeld residuals plotted over time, as well as testing for a trend. In multivariable analysis, interactions were considered. There was no significant deviation from the Cox regression assumption or no significant interactions in multivariable models after the Bonferroni correction for multiple comparisons. For survival analyses, patients with GOS level 1 (who died during hospital stay) were removed from the GOS variable analysis, since this includes the outcome of survival analysis. For Kaplan-Meier analyses of GOS, the follow-up started at hospital discharge. For the Cox regression analysis, GOS was handled as a time-dependent variable, taking effect at hospital discharge.

Parameters for multivariable analysis were selected based on clinical relevance and univariable analyses, taking into account the inbuilt correlations between the variables. Age and EMSE-EAC were not included since age is already included in STESS and EMSE-EAC includes age and CCI, which are considered in the model. Parameters selected for multivariable Cox proportional hazards analysis were STESS>4, GOS levels 2,3,4 and 5 and CCI (0,1-3,>3).

P values <0.05 were considered significant and two-tailed tests were used. Statistical analyses were performed with SPSS software (version 2.0-27.0, IBM Corp, NY, USA) and R version 4.0.3 (Foundation for Statistical Computing, Vienna, Austria).

Results

Mortality and life expectancy

The in-hospital mortality rate of the 62 CSE patients was 8.1%. Mortality rate at one year was 25.8%, at five years 51.6% and at 10 years 64.5%. Of the deaths, 80% occurred during the first five years after CSE onset. Relative survival to the age-adjusted population of Finland at 10 years was 39.3% (95% CI: 26.1-52.2%). Estimated SMR was 5.3 (95% CI: 3.7-6.8). The mean PYLL was 20.9 (median: 16.6; range: 0-57 years) for patients who died during follow-up. Only one deceased patient did not lose any potential years of life.

▼ **Table 3.** Official causes of death during follow-up.

Cause of death	All	CSE period	End of CSE to 1 year	1 to 5 years	5 to 10 years
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Acute or prior brain disorder	12 (30)	0	5 (12.5)	5 (12.5)	2 (5)
Circulatory system	6 (15)	0	2 (5)	2 (5)	2 (5)
Epilepsy-related	4 (10)	1 (2.5)	1 (2.5)	2 (5)	0
Intracranial tumour	4 (10)	1 (2.5)	0	3 (7.5)	0
Respiratory system	3 (7.5)	0	1 (2.5)	1 (2.5)	1 (2.5)
Cancer (no intracranial tumours)	3 (7.5)	1 (2.5)	1 (2.5)	1 (2.5)	0
Digestive system	2 (5)	0	0	1 (2.5)	1 (2.5)
Substance abuse	2 (5)	0	0	1 (2.5)	1 (2.5)
Endocrine system and metabolism	1 (2.5)	1 (2.5)	0	0	0
Urinary system and genitals	1 (2.5)	0	1 (2.5)	0	0
Treatment complications	1 (2.5)	1 (2.5)	0	0	0
Unknown	1 (2.5)	0	0	0	1 (2.5)
Total	40 (100)	5 (12.5)	11 (27.5)	16 (40)	8 (20)

Causes of death

According to the Official Statistics of Finland, the causes of deaths were determined based on forensic autopsy in 12 (30%), clinical autopsy in six (15%) and clinical examination in 22 (55%) cases. Twelve patients (30%) died due to an acute or prior brain disorder. Circulatory system and epilepsy-related causes and intracranial tumours contributed to 35% of deaths. Fifty percent of patients died of causes other than neurological causes. In 39 (97.5%) patients, death was caused by a condition already diagnosed at the time of CSE. One (2.5%) patient died after nine years of follow-up due to a condition that had developed entirely after the CSE episode. The causes of death are fully outlined in *table 3*.

The official cause of death was epilepsy-related in four cases (10%), and only one of these patients died during the CSE period. After reviewing all the death certificates and evaluating the sequel leading to death, we found epilepsy or SE to be an integral part of the events leading to death in another 15 cases (37.5%). These patients had convulsions or SE leading to death due to brain damage, involving infection or adverse effects of the given treatment. In one patient (2.5%), the official cause of death was reported as unknown (*Mors e causa ignota*) after forensic autopsy. However, symptomatic epilepsy and prior SE in the patient's medical history made SUDEP a plausible cause of death. When factoring in all the above-mentioned cases and the official causes of death, epilepsy-related causes were involved in 20 (50%) deaths altogether.

Effect of CSE on mortality

The effect of CSE on survival was analysed using several parameters. In the univariable survival analysis, age ≥65, CCI>0, STESS>4 and EMSE-EAC>15 were found to be risk factors and GOS=5 at discharge a protective factor for survival. The comprehensive results of the univariable survival analysis are presented in *table 4*. The effects of CCI (p=0.001) and GOS (p=0.019) were also demonstrated by Kaplan-Meier curves (*figure 2*).

In the multivariable survival analysis, as seen in *table 5*, STESS>4 and CCI>0 proved to be independent risk factors and GOS>3 a protective factor for survival.

Discussion

This study provides substantial novel information on the long-term outcome of CSE patients with a follow-up of 10 years. The mortality rate of patients with an in-hospital mortality rate of less than 10% increased up to 65% at 10 years after an episode of CSE. The lifetime of patients with CSE was far below the expected lifetime, with deceased patients losing more than 20 years of potential life on average, and CSE was associated with a >five-fold increased mortality rate compared to the average population. Half of the official causes of death were not neurological. On closer examination, it appeared that epilepsy was contributing to death in around 50% of cases. The severity of CSE, high number of comorbidities

▼ **Table 4.** Univariable survival analysis for all variables at 10 years after convulsive status epilepticus (CSE).

Variable		All Cases	Dead	Alive		95%CI	95%CI	
		n (%)	*n* (%)	*n* (%)	HR	Min	Max	*p*
Demographics		**62 (100)**	**40 (65)**	**22 (35)**				
Gender	Male	32 (52)	23 (57)	9 (40)	1.6	0.86	2.91	0.14
Age	≥65	17 (27)	16 (40)	1 (5)	**2.8**	1.50	5.39	**0.001**
Epilepsy	Yes	38 (61)	22 (55)	16 (46)	0.67	0.36	1.24	0.20
CCI	0 (ref)	17 (27)	6 (16)	11 (50)	1			
	1-3	40 (65)	29 (73)	11 (50)	**3.0**	1.32	6.87	**0.009**
	>3	5 (8)	5 (13)	0(0)	**8.4**	2.49	28.34	**<0.001**
CSE characteristics								
Aetiology	Acute symptomatic (ref)	31 (50)	17 (43)	14 (64)	1			0.69
	Remote symptomatic	18 (29)	14 (35)	4 (18)	1.4	0.70	2.76	0.35
	Progressive symptomatic	5 (8.1)	4 (10)	1 (5)	1.7	0.59	5.11	0.32
	Unknown	8 (13)	5 (13)	3 (14)	1.2	0.46	3.25	0.69
STESS	>4	9 (15)	9 (23)	0 (0)	**5.3**	2.37	11.76	**<0.001**
STESS	2 (ref)	29 (47)	15 (38)	14 (64)	1			
	3	16 (26)	9 (23)	7 (32)	0.90	0.40	2.00	0.80
	4	8 (13)	7 (18)	1 (5)	1.7	0.72	4.18	0.22
	5	9 (15)	9 (23)	0 (0)	**5.7**	2.40	13.65	**<0.001**
EMSE-EAC	>27	24 (39)	16 (40)	8 (36)	1.2	0.62	2.15	0.64
EMSE-EAC	>15	45 (73)	33 (83)	12 (55)	**2.2**	1.05	4.62	**0.036**
EMSE-EAC	0-15 (ref)	17 (27)	7 (18)	10 (45)	1			
	16-25	17 (27)	15 (38)	2 (9)	**2.9**	1.26	6.63	**0.012**
	≥26	28 (45)	18 (45)	10 (45)	1.8	0.82	4.11	0.13
Pre-status period	Yes	13 (21)	6 (15)	7 (32)	0.6	0.28	1.30	0.20
SE onset	Intermittent	22 (35)	11 (28)	11 (50)	0.55	0.28	1.08	0.083*
Refractoriness	SRSE	28 (45)	17 (43)	11 (50)	0.94	0.52	1.73	0.85
Treatment and complications								
Anaesthetic treatment	Only propofol	48 (77)	32 (80)	16 (73)	0.89	0.49	1.65	0.72
Burst suppression	Yes	25 (40)	15 (38)	10 (45)	0.83	0.45	1.54	0.55
Use of vasopressors	Yes	43 (69)	27 (68)	16 (73)	1.1	0.56	2.08	0.81
Mechanical ventilation	Yes	54 (87)	35 (88)	19 (86)	1.1	0.45	2.88	0.80
CBI	>3	28 (45)	16 (40)	12 (55)	0.88	0.48	1.62	0.68
CBI	Continuous variable	62 (100)	40 (100)	22 (100)	1.1	0.92	1.26	0.37

▼ **Table 4.** Univariable survival analysis for all variables at 10 years after convulsive status epilepticus (CSE) (*continued*).

Variable		All Cases	Dead	Alive		95%CI	95%CI	
		n (%)	*n* (%)	*n* (%)	HR	Min	Max	*p*
Infections	Yes	53 (85)	35 (88)	18 (82)	1.7	0.65	4.20	0.29
Outcome at hospital discharge								
GOS (2-5) (time-dependent)	>3	37 (60)	20 (40)	17 (77)	0.535	0.28	1.03	0.062*
GOS (time-dependent)	2 (ref)	5 (8)	4 (10)	1 (5)	1			
	3	15 (24)	11 (28)	4 (18)	0.65	0.21	2.02	0.460
	4	30 (48)	18 (45)	12 (55)	0.46	0.16	1.34	0.156
	5	7 (11)	2 (5)	5 (23)	**0.14**	0.03	0.78	**0.025**
Condition (time-dependent)	Worse than baseline	38 (61)	29 (73)	9 (41)	1.8	0.98	3.39	0.060*
Delays		time h/ (IQR)	time h/ (IQR)	time h/ (IQR)				
Onset to initial treatment		0.5 (0.8)	0.5 (0.8)	0.5 (0.57)	0.95	0.56	1.67	0.79
Onset to diagnosis		1.8 (3.0)	2.0 (2.7)	1.2 (3.4)	0.92	0.53	2.15	0.77
Onset to second-stage treatment		2.6 (2.9)	2.7 (2.2)	2.3 (4.5)	0.71	0.26	2.54	0.42
Onset to tertiary hospital		2.4 (2.9)	2.4 (2.0)	2.9 (4.0)	1.1	0.47	3.33	0.80
Onset to burst suppression		16.5 (18.5)	13.5 (16.8)	1.0 (23.8)	1.3	0.09	5.86	0.73
Onset to seizure freedom		5.6 (0.15)	4.2 (13.5)	13.0 (8.1)	0.87	0.57	1.31	0.48
Onset to consciousness		16.9 (10.6)	4.5 (19.1)	19.8 (19.7)	0.75	0.40	1.46	0.40
Length of anaesthetic treatment		14.0 (5.9)	10.3 (10.0)	16.3 (5.3)	1.1	0.34	2.85	0.90
Length of ICU treatment		12.8 (8.7)	10.7 (15.7)	23.8 (2.6)	1.1	0.57	2.24	0.79

and poor condition at hospital discharge at the time of CSE were independent risk factors for mortality during the 10-year follow-up period.

This retrospective cohort study was conducted in a single tertiary centre. HUS provides tertiary care for the most challenging CSE patients in southern Finland and only patients independent in activities of daily life are treated in HUS. Due to the long follow-up period for the cohort, the definition of SE changed over time, from when the study was initiated. Currently, CSE is defined as seizure lasting for at least five minutes [1] whereas, at the time of data collection, the defining time period was 30 minutes. These factors lead to a degree of sampling bias, a higher percentage of SRSE cases, and a smaller than expected cohort size based on the population size and incidence of SE from previous reports.

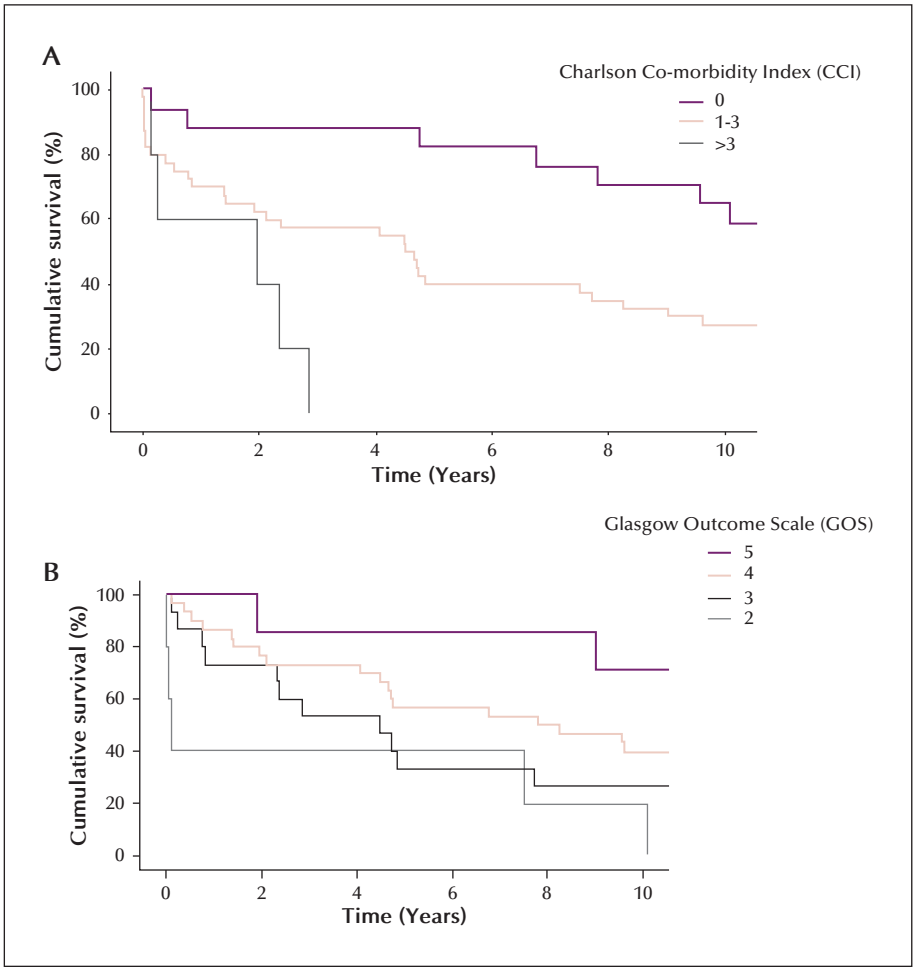
By definition, retrospective studies entail a risk of reporting bias. However, data availability in this study was laudable. Mortality statistics and death certificates were all retrievable from the Official Statistics of Finland, and variables associated with the CSE period, demographics and outcome information from the hospital patient database, except for one patient's epilepsy history information. Moreover, the records of the Finnish EMS and in the electronic patient database are very accurate.

Unlike today, EEG recording was not routinely available outside office hours in the HUS ED at the time of data collection. Consequently, the EMSE-EAC score had to be used instead of EMSE-EACE [16].

These limitations are to be considered when interpreting the results of this study.

Mortality and life expectancy

The rate of long-term mortality at 65% in this study is considerably higher than in prior studies with a



■ **Figure 2.** Kaplan-Meier curves demonstrating the effects of the Charlson Comorbidity Index (CCI) (p=0.001) and the Glasgow Outcome Scale (GOS= (p=0.019) on mortality during the 10-year follow-up. For the GOS, follow-up was started at the time of hospital discharge.

▼ **Table 5.** Multivariable survival analysis at 10 years after convulsive status epilepticus (CSE).

Variable		HR	95%CI min	95% CI max	*p*
STESS	>4	**5.0**	1.83	13.46	**0.002**
CCI	0 (ref)	1			
	1-3	**2.9**	1.23	6.74	**0.015**
	>3	**6.3**	1.70	23.60	**0.006**
GOS (time-dependent)	2 (ref)	1			
	3	0.40	0.12	1.28	0.122
	4	**0.33**	0.11	0.99	**0.048**
	5	**0.13**	0.02	0.72	**0.019**

follow-up of at least 10 years, with mortality rates ranging from 17% to 43% [5-7, 13]. This difference might be partly due to the fact that most of these studies also included children, whose overall estimated mortality after CSE is substantially lower than in adults [25]. Further, the majority of these prior studies were population-based, and the higher mortality rate in this present study might reflect the tertiary hospital setting, where the proportion of difficult-to-treat cases with greater risk of death is higher than in the general population.

The 10-year mortality rate is surprisingly high considering that several parameters would have suggested otherwise. premorbid condition was good (GOS 4 or 5) in over 90% of the patients, which would have predicted lower mortality [26-28]; over 70% of the patients were younger than 65 years of age, which should indicate better outcomes [7, 13, 18]; nearly 60% had previously diagnosed epilepsy, which has also proven to be a protective factor [12, 14]; a good functional outcome (GOS 4-5) at hospital discharge was reached by 60% of the patients, which, according to prior research, suggests a favourable outcome [8, 14]; finally, the in-hospital mortality rate remained below 10%, which is relatively low compared with other studies in the literature [8-10].

The patients in our study had a >five-fold increased risk of death in comparison with the age-matched population in Finland. The risk of mortality was greater than in previous studies, which have demonstrated a 2.6 to 2.8-fold [6, 7] increased risk of death related to SE. Furthermore, the deceased patients in this cohort lived for >20 years less on average relative to their age and sex-adjusted life expectancy. Prior research on life expectancy or PYLL among CSE patients is, to our knowledge, non-existent and only a few studies could be found regarding patients with epilepsy (PWE), for comparison. These studies suggest that PWEs have a decreased life expectancy, especially regarding epilepsies with symptomatic aetiology. In this aetiological subgroup, the PYLL is around 7 to 13 [29, 30]. However, other aetiological subgroups in both studies were found to have minimal changes in life expectancy [29, 30] or to live even longer than expected [29]. In other words, CSE seems to be a major hazard for patients also in the long term. This raises the question as to whether SE is merely a reflection of patients' poor overall condition rather than solely the CSE episode affecting the prognosis.

Causes of death

The most common official causes of death in this patient cohort were disorders of the brain and circulatory system. Logroscino *et al*. found fairly similar results in their study in which cardiovascular or cerebrovascular diseases were the cause of death in the majority of SE patients based on a 10-year follow-up period [6]. Other studies have reported cardiovascular causes or malignancies [13] and SE complications or comorbidities [22] responsible for most deaths during follow-up. The significant role of comorbidities contributing to the cause of death was also evident in this study. It is notable that the burden of comorbidities was already present at the time of CSE, and in most cases, one of these comorbidities was ultimately the underlying cause of death.

The official cause of death was epilepsy-related in 10% of cases. When factoring in all cases with epilepsy-related causes, the proportion was as high as 50%. In conclusion, after evaluation of the death certificates, epilepsy-related causes were deemed to play a major role in the deaths of the patients. According to the Official Statistics of Finland, 115 deaths were registered with the ICD-10 codes G40 or G41 in Finland in 2019. This accounts for 2.1‰ of all registered deaths in Finland that year [31]. Considering these statistics, the epilepsy-related mortality in this study is substantially higher than expected.

In two recent studies [32, 33], the authors reported that although epilepsy-related causes were still the leading causes of death, PWEs die increasingly more from other causes. In both studies, there was an overall increase in neurological burden and other neurological disorders as the underlying cause of death. Considering SE specifically, its role as a contributing factor seemed to remain essentially the same during the study period [32]. Although the focus of these studies was epilepsy deaths in general rather than SE, some similarities can be identified. A large burden of neurological morbidity was evident in this study since nearly 60% of the patients had prior structural brain abnormalities at the time of CSE, half the patients died of neurological causes, and the portion of epilepsy-related causes was prominent when considering all-cause mortality.

Effect of CSE on mortality

Several factors were found to independently affect the outcome of patients at 10 years after an episode of CSE: having comorbidities (CCI), STESS >4, and poor functional outcome at hospital discharge (GOS). Old age and a high EMSE score were also risk factors.

CCI [23] is a well-established scale for evaluating the effect of comorbidities on patients' outcome in general. Considering SE patients in previous studies, CCI shows some predictive value regarding short-term mortality [17, 34]. In particular, CCI scores for tumours, vital organ diseases (heart, liver, kidney) and

diabetes are associated with in-hospital mortality [26, 35]. This association is in parallel with long-term mortality, however, only a few studies have elaborated and confirmed the association between comorbidities or CCI and long-term mortality [5, 9]. Similarly, cancer, heart diseases and chronic kidney failure have been found to be risk factors for mortality at 10 years after SE [5]. This study certifies the substantial burden of underlying diseases contributing to the final outcome based on long-term follow-up.

STESS [15] was originally developed to predict in-hospital mortality associated with SE. Regarding previous research, the relevance of STESS on long-term mortality seems somewhat contradictory. STESS, with a cut-off of 3 and 4, has been associated with poor long-term outcome [11, 12, 14]. However, in one study, STESS was not a risk factor for mortality but some of its components were [10], and a few studies did not find any significance at all [8, 9, 36]. Follow-up periods in the above-mentioned studies varied between 12 weeks and 2.5 years, falling considerably below the follow-up period of this study, demonstrating the effect of STESS on prognosis at even up to 10 years.Functional outcome at discharge is a significant prognostic factor, which has been proven in a few previous studies. Rodin *et al*. found that a score of $\geq$2 on the modified Rankin Scale at discharge predicted long-term mortality [8]. Equally, a prior study using the same cohort as the current one showed that GOS>3 was a protective factor and worse-than-baseline condition was a risk factor for mortality for up to one year [14]. In this study, the effect seems to remain as time passes.

Age has proven to be a significant predictor for long-term mortality in numerous studies [7, 13, 18, 37]. In this study, patients over the age of 65 were more likely to die. This was partially predictable since the follow-up was 10 years, and these patients would have reached an old age by the end of the study. However, hardly any of the deceased patients reached their reference life expectancy.

There are several variations of the EMSE [16] regarding the factors included. EMSE-EACE, as a predictor for long-term outcome, has been established in a few studies [9, 12, 38]. Unfortunately, it was not applicable in our study setting, and the EMSE-EAC was used instead. Studies on short-term mortality of up to one month have shown a predictive value of EMSE-EAC with a variety of cut-offs between 27 and 37 [16, 19, 39]. Only one previous study demonstrated EMSE-EAC to be significant in predicting long-term mortality with a cut-off of 27 and a median follow-up of 13 months [12]. In this present study, an EMSE-EAC score >15 was shown to be predictive of long-term mortality, rather than 27. This further underlines EMSE as a useful tool to predict the outcome of SE.

Aetiology has been found to be associated with long-term outcome in multiple studies [37], with acute symptomatic [7, 13] and progressive symptomatic [7] aetiologies being the most predictive of poor long-term outcome. Surprisingly, aetiology was not found to be a significant predictor of long-term mortality in this study. Furthermore, SRSE was not a risk factor in this study. As stated previously, long-term outcome may not be explained by single factors related to the CSE episode itself, but rather by overall condition. Further, refractoriness does not always result in worse outcomes [40].

Conclusion

The rate of mortality at 10 years was high following CSE, and the deceased patients lost a considerable number of potential years of life. Epilepsy-related causes had a significant, possibly underestimated, impact on mortality. Comorbidities existing at the time of CSE appeared to have a significant effect on mortality since the underlying cause of death could often be traced back to them. CSE characteristics indicative of the patients' overall condition at the time of CSE, such as comorbidities, functional state after CSE and age, were significant regarding long-term outcome. Therefore, in addition to treating the CSE itself, the comorbid conditions should be considered and adequately treated. Factors such as treatments, delays and complications, seem to lose their significance over time. This study demonstrates that after a sufficiently long follow-up period, the variables studied at the time of CSE do not seem to affect the prognosis of patients. It seems that a high mortality rate is mainly explained by a high burden of other diseases, and for the majority of patients, SE might act merely as an indicator of high disease burden, which may be fatal in the short term. Whether a single acute symptomatic seizure of short duration (<5 min) also acts as a similar indicator is unknown and further study is required. ■

Key points

- The 10-year mortality rate of CSE patients was notably high, up to 64.5%.
- On average, the life expectancy of deceased patients was reduced by >20 years.
- The official cause of death was not neurological in a half of the cases.
- Epilepsy-related causes were identified for half of the deaths.
- Age, comorbidities, functional outcome at discharge, EMSE and STESS were significant predictive factors for long-term outcome.

Supplementary material.

Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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This study is not a clinical trial and therefore is not registered as one. Restrictions apply to the availability of these data, which were used under license for this study.

References

1. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, *et al*. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015; 56(10): 1515-23.

2. [No authors listed]. Guidelines for epidemiologic studies on epilepsy. Commission on epidemiology and prognosis, International League Against Epilepsy. *Epilepsia* 1993; 34(4): 592-6.

3. Shorvon S, Sen A. What is status epilepticus and what do we know about its epidemiology? *Seizure* 2020; 75: 131-6.

4. Chin RF, Neville BG, Scott RC. A systematic review of the epidemiology of status epilepticus. *Eur J Neurol* 2004; 11(12): 800-10.

5. Tiamkao S, Saybungkla P, Sirikarn P, Sawanyawisuth K. Predictors of long-term mortality in status epilepticus. *Epilepsy Behav* 2018; 84: 114-7.

6. Logroscino G, Hesdorffer DC, Cascino G, Hauser WA. Status epilepticus without an underlying cause and risk of death: a population-based study. *Arch Neurol* 2008; 65(2): 221-4.

7. Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. Long-term mortality after a first episode of status epilepticus. *Neurology* 2002; 58(4): 537-41.

8. Rodin E, Krogstad MH, Aukland P, Lando M, Møller HS, Gesche J, *et al*. High long-term mortality after incident status epilepticus in adults: results from a population-based study. *Epilepsia* 2019; 60(1): 33-41.

9. Møller HS, Rodin E, Aukland P, Lando M, Christiansen EB, Beier CP. Epidemiology-based mortality score is associated with long-term mortality after status epilepticus. *Neurocrit Care* 2019; 31(1): 135-41.

10. Aukland P, Lando M, Vilholm O, Christiansen EB, Beier CP. Predictive value of the Status Epilepticus Severity Score (STESS) and its components for long-term survival. *BMC Neurol* 2016; 16(1): 213.

11. Madžar D, Geyer A, Knappe RU, Gollwitzer S, Kuramatsu JB, Gerner ST, *et al*. Association of seizure duration and outcome in refractory status epilepticus. *J Neurol* 2016; 263 (3): 485-91.

12. Atmaca MM, Bebek N, Baykan B, Gökyiğit A, Gürses C. Predictors of outcomes and refractoriness in status epilepticus: a prospective study. *Epilepsy Behav* 2017; 75: 158-64.

13. Ristić AJ, Sokić D, Trajković G, Janković S, Vojvodić NM, Bascarević V, *et al*. Long-term survival in patients with status epilepticus: a tertiary referral center study. *Epilepsia* 2010; 51 (1): 57-61.

14. Tuppurainen KM, Ritvanen JG, Mustonen H, Kämppi LS. Predictors of mortality at one year after generalized convulsive status epilepticus. *Epilepsy Behav* 2019; 101(Pt B): 106411.

15. Rossetti AO, Logroscino G, Bromfield EB. A clinical score for prognosis of status epilepticus in adults. *Neurology* 2006; 66(11): 1736-8.

16. Leitinger M, Höller Y, Kalss G, Rohracher A, Novak HF, Höfler J, *et al*. Epidemiology-based mortality score in status epilepticus (EMSE). *Neurocrit Care* 2015; 22(2): 273-82.

17. Ciurans J, Grau-López L, Jiménez M, Fumanal A, Misis M, Becerra JL. Refractory status epilepticus: Impact of baseline comorbidity and usefulness of STESS and EMSE scoring systems in predicting mortality and functional outcome. *Seizure* 2018; 56: 98-103.

18. Claassen J, Lokin JK, Fitzsimmons BF, Mendelsohn FA, Mayer SA. Predictors of functional disability and mortality after status epilepticus. *Neurology* 2002; 58(1): 139-42.

19. Sairanen JJ, Kantanen AM, Hyppölä HT, Kälviäinen RK. Outcome of status epilepticus and the predictive value of the EMSE and STESS scores: a prospective study. *Seizure* 2020; 75: 115-20.

20. Giovannini G, Monti G, Tondelli M, Marudi A, Valzania F, Leitinger M, *et al*. Mortality, morbidity and refractoriness prediction in status epilepticus: comparison of STESS and EMSE scores. *Seizure* 2017; 46: 31-7.

21. Hawkes MA, English SW, Mandrekar JN, Rabinstein AA, Hocker S. Causes of death in status epilepticus. *Crit Care Med* 2019; 47(9): 1226-31.

22. Sirikarn P, Pattanittum P, Sawanyawisuth K, Tiamkao S. Causes of death in patients with status epilepticus. *Epilepsy Behav* 2019; 101(Pt B): 106372.

23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5): 373-83.

24. Kämppi L, Ritvanen J, Strbian D, Mustonen H, Soinila S. Complication Burden Index-A tool for comprehensive evaluation of the effect of complications on functional outcome after status epilepticus. *Epilepsia* 2018; 59(Suppl 2): 176-81.

25. Neligan A, Noyce AJ, Gosavi TD, Shorvon SD, Köhler S, Walker MC. Change in mortality of generalized convulsive status epilepticus in high-income countries over time: a systematic review and meta-analysis. *JAMA Neurol* 2019; 76 (8): 897-905.

26. Belluzzo M, Furlanis G, Stragapede L, Monti F. Role of comorbidities and in-hospital complications in short-term status epilepticus outcome. *Clin Neurol Neurosurg* 2017; 154: 13-8.

27. Kantanen AM, Kälviäinen R, Parviainen I, Ala-Peijari M, Bäcklund T, Koskenkari J, *et al*. Predictors of hospital and one-year mortality in intensive care patients with refractory status epilepticus: a population-based study. *Crit Care* 2017; 21(1): 71.

28. González-Cuevas M, Santamarina E, Toledo M, Quintana M, Sala J, Sueiras M, *et al*. A new clinical score for the prognosis of status epilepticus in adults. *Eur J Neurol* 2016; 23 (10): 1534-40.

29. Granbichler CA, Zimmermann G, Oberaigner W, Kuchukhidze G, Ndayisaba JP, Taylor A, *et al*. Potential years lost and life expectancy in adults with newly diagnosed epilepsy. *Epilepsia* 2017; 58(11): 1939-45.

30. Gaitatzis A, Johnson AL, Chadwick DW, Shorvon SD, Sander JW. Life expectancy in people with newly diagnosed epilepsy. *Brain* 2004; 127(Pt 11): 2427-32.

31. *Statistic Finlands free-of-charge databases*. https://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin__ter__ksyyt/statfin_ksyyt_pxt_11bv.px/table/

32. DeGiorgio CM, Curtis AT, Hertling D, Kerr WT, Markovic D. Changes in epilepsy causes of death: a US population study. *Acta Neurol Scand* 2021; 144(5): 478-85.

33. DeGiorgio CM, Curtis A, Carapetian A, Hovsepian D, Krishnadasan A, Markovic D. Why are epilepsy mortality rates rising in the United States? A population-based multiple cause-of-death study. *BMJ Open* 2020; 10(8): 035767.

34. Alvarez V, Januel M, Burnand Y, Rossetti AO. Role of comorbidities in outcome prediction after status epilepticus. *Epilepsia* 2012; 53(5): 89-92.

35. Mendiratta P, Dayama N, Wei JY, Prodhan P, Prodhan P. Status epilepticus among older adults in the United States. *Geriatrics (Basel)* 2019; 4(3): 45.

36. Kantanen A-M, Reinikainen M, Parviainen I, Kälviäinen R. Long-term outcome of refractory status epilepticus in adults: a retrospective population-based study. *Epilepsy Res* 2017; 133: 12-21.

37. Sculier C, Gaínza-Lein M, Sánchez Fernández I, Loddenkemper T. Long-term outcomes of status epilepticus: a critical assessment. *Epilepsia* 2018; 59(Suppl 2): 155-69.

38. Santamarina E, Parejo-Carbonell B, Abraira L, Gutiérrez-Viedma A, Fonseca E, Seijo I, *et al*. Status epilepticus without impairment of consciousness: long-term outcomes according to duration. *Epilepsy Behav* 2021; 120: 108007.

39. Ulvin LB, Taubøll E, Olsen KB, Heuser K. Predictive performances of STESS and EMSE in a Norwegian adult status epilepticus cohort. *Seizure* 2019; 70: 6-11.

40. Alvarez V, Drislane FW. Is favorable outcome possible after prolonged refractory status epilepticus? *J Clin Neurophysiol* 2016; 33(1): 32-41.

TEST YOURSELF

(1) Which of the following is true regarding life expectancy of the deceased patients in this cohort?

A. Convulsive status epilepticus did not have an impact on life expectancy
B. The patients lost on average 10 potential years of life
C. Only one patient reached their reference life expectancy.

(2) Which of the following are the most common causes of death among convulsive status epilepticus patients based on long-term follow-up?

A. Respiratory causes
B. Treatment complications
C. Acute or prior brain disorders

(3) What is the significance of comorbidities regarding the outcome of status epilepticus?

A. Comorbidities have been proven to associate with poor outcome
B. Comorbidities existing at the time of generalized convulsive status epilepticus are unlikely causes of death in the long term
C. Comorbidities scored according to the Charlson Comorbidity Index have not been shown to be a risk factor for long-term mortality

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.