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Predictors of mortality at one year after generalized convulsive status epilepticus

Kati Marjatta Tuppurainen [a,*], Jaakko Gabriel Ritvanen [a], Harri Mustonen [b], Leena Sinikka Kämppi [a]

[a] Clinical Neurosciences, Neurology, University of Helsinki and Department of Neurology, Helsinki University Central Hospital, Finland
[b] Department of Surgery, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

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ABSTRACT

Background: Status epilepticus (SE) is a life-threatening neurologic emergency, which requires prompt medical treatment. Little is known of the long-term survival of SE. The aim of this study was to investigate which factors influence 90 days and 1-year mortality after SE.
Materials and methods: This retrospective study includes all consecutive adult (>16 years) patients (N = 70) diagnosed with generalized convulsive SE (GCSE) in Helsinki University Central Hospital (HUCH) emergency department (ED) over 2 years. We defined specific factors including patient demographics, GCSE characteristics, treatment, complications, delays in treatment, and outcome at hospital discharge and determined their relation to 90 days and 1-year mortality after GCSE by using logistic regression models. Survival analyses at 1 year after GCSE were performed with Cox proportional hazards regression analysis.
Results: In-hospital mortality was 7.1%. Mortality rate was 14.3% at 90 days and 24.3% at 1 year after GCSE. In the univariate logistic regression analysis, Status Epilepticus Severity Score > 4 (STESS) (ODDS = 7.30, $p = 0.012$), worse-than-baseline condition at hospital discharge (ODDS = 3.5, $p = 0.006$), long delays in attaining seizure freedom (ODDS = 2.2, $p = 0.041$), and consciousness (ODDS = 3.4, $p = 0.014$) were risk factors for mortality at 90 days whereas epilepsy (ODDS = 0.2, $p = 0.014$) and Glasgow Outcome Scale (GOS) >3 at hospital discharge (ODDS = 0.05, $p = 0.006$) were protective factors. Risk factors for mortality at 1 year were STESS >4 (ODDS = 5.1, $p = 0.028$), use of vasopressors (ODDS = 8.2, $p = 0.049$), and worse-than-baseline condition at discharge (ODDS = 7.8, $p = 0.010$) while GOS >3 (ODDS = 0.2, $p = 0.005$) was protective.
The univariate survival analysis at 1 year confirmed the significant findings regarding parameters STESS >4 (Hazard ratio (HR) = 4.1, $p = 0.009$), worse-than-baseline condition (HR = 6.2, $p = 0.015$), GOS >3 (HR = 0.2, $p = 0.004$) at hospital discharge and epilepsy (HR = 0.4, $p = 0.044$). Additionally, diagnostic delay over 6 h (HR = 3.8, $p = 0.022$) and Complication Burden Index (CBI) as an ordinal variable (0–2, 3–6, >6) (HR = 2.7, $p = 0.027$) were predictive for mortality.
In the multivariate survival analysis, STESS > 4 (HR = 5.1, $p = 0.007$), CBI (HR = 3.2, $p = 0.025$, ordinal variable), diagnostic delay over 6 h (HR = 7.2, $p = 0.003$), and worse-than-baseline condition at hospital discharge (HR = 5.8, $p = 0.027$) were all independent risk factors for mortality at 1 year.
Conclusions: Severe form of SE, delayed recognition of GCSE, high number of complications during treatment period, and poor condition at hospital discharge are all independent predictors of long-term mortality. Most of these factors are also associated with mortality at 90 days, though at that point, delays in treatment seem to have a greater impact on prognosis than at 1 year.
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1. Introduction

Status epilepticus (SE) is a life-threatening medical emergency, which requires prompt medical treatment and is associated with substantial morbidity and mortality. The incidence of SE ranges from 10 to 20 per 100,000 and mortality between 1.9 and 40% in published studies [1]. Factors related to poor short-term outcome include old age, symptomatic etiology, refractoriness, comorbidities, poor premorbid

Abbreviations: ADL, active daily living; CBI, Complication Burden Index; CCI, Charlson Comorbidity Index; DA, data availability; EMS, emergency medical service; EMSE, epidemiology-based mortality score in status epilepticus; EMSE-EACE, epidemiology-based mortality score in status epilepticus, etiology-age-comorbidity-EEG; GOS, Glasgow Outcome Scale; HUCH, Helsinki University Central Hospital; L_{WAS}, the weighted accuracy score; STESS, Status Epilepticus Severity Score.

* Corresponding author at: Majavatie 10 A 19, Helsinki, Finland.
E-mail addresses: kati.tuppurainen@hus.fi (K.M. Tuppurainen), jaakko.ritvanen@hus.fi (J.G. Ritvanen), Harri.mustonen@helsinki.fi (H. Mustonen), leena.kamppi@hus.fi (L.S. Kämppi).

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condition, long duration of SE, and complications and delays in the treatment [2–12]. Most of these outcome predictors have been incorporated in outcome scores Status Epilepticus Severity Score (STESS) [13], modified STESS (mSTESS) [8], and epidemiology-based mortality score in status epilepticus (EMSE) [14]. These scores have been developed for the in-hospital mortality prediction of SE. The predictive value of these scores has been externally validated, although the optimal predictive cutoff for STESS varies between the studies [15–17].

Up to date, the knowledge of long-term survival of SE is considerably more limited than that of short-term mortality. A recent review of altogether 37 studies reported a substantial long-term mortality with a wide range [18]. Ninety days mortality ranged from 14% to 50% [18–20], and mortality after at least 1-year of follow-up ranged from 23% to 57% [6,18,21]. There are only a few studies regarding factors affecting long-term mortality after SE, and the results are somewhat inconsistent. In most studies, symptomatic or potentially fatal etiology, older age, long duration of SE, refractoriness, and dependence in active daily living (ADL) functions have been shown to predict poor long-term outcome after SE [6,18,22,23], however, there are also opposite results [24]. The predictive value of STESS for long-term mortality remains unconfirmed, since in some studies, it does not validate as a long-term predictor [18,24,25], although there are also promising results [22,26,27]. On the other hand, EMSE score has been associated with poor long-term outcome in one prospective study [27]. Still, the association of delays and complications in the treatment with long-term mortality remains undefined.

The aim of this study was to investigate which factors affect mortality of generalized convulsive SE (GCSE) after 90 days and 1 year.

2. Materials and methods

2.1. Study design and setting

This is a retrospective cohort study performed in Helsinki University Central Hospital (HUCH). This study conforms to the Finnish legislation concerning medical research, and the permission was granted by the HUCH Department of Neurology.

Helsinki University Central Hospital is a tertiary hospital serving a population of 1.4 million, and the emergency department (ED) offers 24 h neurological emergency service to the entire hospital district. In addition to HUCH, the hospital district is served by seven regional hospitals with EDs run by internists and several healthcare centers. The local emergency medical service (EMS) is instructed to transport any patient independent in daily living with GCSE primarily to HUCH ED. At the time of the study period, EMS had the possibility to administer first- and third-stage treatments of SE, and second-stage treatment was administered in the ED.

2.2. Definition of GCSE

At the time of material collection, established SE was defined as continuous seizures lasting over 30 min, several recurrent seizures without return of consciousness or occurrence of more than four seizures within any 1 h irrespective of return of consciousness in between. Patients having a convulsive seizure at any point of the SE period were considered as having convulsive SE (CSE). Patients with impaired consciousness, either primarily or secondarily, were considered as having generalized SE (GSE).

2.3. Selection of participants

This study includes 70 consecutive adult patients (≥16 years) diagnosed with GCSE and treated in the HUCH ED between January 2002 and December 2003.

The patients were identified in the HUCH electronic patient database by the International Classification of Diseases Tenth Revision (ICD-10) code G41 (SE), yielding a total of 87 patients. Patients not meeting the criteria of GCSE were excluded. A total of 70 patients with GCSE were eligible for the study.

2.4. Data collection

Clinical data were collected by a trained medical doctor from the original medical records and recorded into an electronic database. Patient identification information was removed before further analyses.

Patient demographics, GCSE characteristics, parameters for treatment and complications, and measures of outcome were collected for all cases. These parameters are presented in Table 1. In addition, we identified nine specific delay parameters in the management of GCSE, which are presented in Table 2. For determining the accuracy and reliability of the collected time parameters, we calculated the weighted accuracy score (L_{WAS}) and the data availability (DA), using the method developed for evaluation of retrospective delay materials [28].

Table 1
Patient demographics, GCSE characteristics, parameters for treatment, complications and outcome in the study material.

Variable		N	%
All		70	100
Demographics			
Gender	Male	35	50
	Female	35	50
Age under 65	Yes	51	72.9
	No	19	27.1
Epilepsy	Yes	46	65.7
	No	23	32.9
	Unknown	1	1.4
Comorbidity (CCI)	0	18	25.7
	1	16	22.9
	2	18	25.7
	3	10	14.3
	>3	8	11.4
Premorbid GOS	1–3	5	7
GCSE characteristics			
STESS	2	35	152.2
	3	16	69.6
	4	10	43.5
	5	9	39.1
Prestatus period	Yes	14	20.0
	No	56	80.0
SE onset	Continuous	45	64.3
	Intermittent	25	35.7
Refractoriness	Non-SRSE	38	54.3
	SRSE	32	45.7
Treatment and complications			
Anesthetic treatment	No anesthesia	8	11.4
	Only propofol	56	80
	Multiple anesthetics	6	8.6
Burst-suppression obtained	Yes	30	42.9
	No	40	57.1
Complication burden index (CBI)	0–3	38	54.3
	>3	32	45.7
Use of vasopressors	Yes	51	72.9
	No	19	27.1
Mechanical ventilation	Yes	62	88.6
	No	8	11.4
Infections	Yes	61	87.1
	No	9	12.9
Outcome			
GOS at discharge	≤3	28	40
	>3	42	60
Condition at discharge	Worse-than-baseline	41	58.6
	Baseline	29	41.4
In-hospital mortality	Yes	5	7.1
	No	65	92.9
90 d mortality	Yes	10	14.3
	No	60	85.7
1 year mortality	Yes	17	24.3
	No	53	75.7

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Table 2
Delay parameters and the delays in the treatment.

Variable	N	%	Time	Min	Max	DA	L_{WAS}
All cases	70	100	Median			%	
Delays in the treatment							
Onset-to-initial-treatment	67	95.7	30 min	0 min	8 h 5 min	97.0	1.8
Onset-to-diagnosis	70	100	1 h 48 min	6 min	60 h 6 min	97.1	1.5
Onset-to-second-stage-medication	67	95.7	2 h 40 min	30 min	61 h 54 min	98.5	1.6
Onset-to-tertiary-hospital (HUCH)	70	100	2 h 25 min	37 min	277 h 40 min	98.6	1.5
Onset-to-burst-suppression	30	42.9	14 h 42 min	5 h 5 min	137 h 50 min	100	1.5
Onset-to-seizure-freedom	70	100	5 h 15 min	26 min	533 h 15 min	98.6	1.6
Onset-to-consciousness	61	87.1	42 h 45 min	2 h 40 min	444 h 40 min	96.7	1.4
Length-of-the-anesthesia-treatment	62	88.5	38 h	3 h 35 min	238 h 52 min	98.4	1.1
Length-of-the-ICU-treatment	63	90	58 h 40 min	7 h 45 min	520 h 25 min	100	1.1

Outcome at hospital discharge was collected from medical records. Long-term mortality up to 1 year was gathered from the causes of death — register maintained by Official Statistics of Finland.

Missing events, e.g., no burst-suppression (BS), events happening during prestatus period, or unknown data were excluded from the final analysis. The missing data information is presented in Online Table 1.

2.5. Definitions of measures

Age of 65 years was selected as the classification basis for age as a grouping variable. Only patients with previously diagnosed epilepsy were considered as having epilepsy, previous epilepsy serving as surrogate for etiology of GCSE. Comorbidity was scored according to Charlson Comorbidity Index (CCI) [29]. Underlying etiologies for GCSE were not scored in CCI. Status Epilepticus Severity Score was calculated for all patients [13]. Seizures occurring up to 48 h prior to GCSE onset were referred to as prestatus period seizures. Seizures lasting at least 30 min clinically were defined as continuous. All other types of seizures were considered as intermittent. Patients' seizures failing to respond to first- or second-stage treatment were considered as refractory SE (RSE). Status epilepticus continuing or recurring 24 h or more after the onset of anesthesia was considered as superrefractory SE (SRSE). The anesthetic treatment was grouped as no anesthesia, only propofol or multiple anesthetics. For the evaluation of complications during treatment period, the Complication Burden Index (CBI) with a cutoff point of >3 and as a continuous variable were used [9]. Functional outcome at hospital discharge was considered good when condition returned to baseline and Glasgow Outcome Scale (GOS) was >3.

The onset of GCSE was defined as the beginning of the first seizure, fulfilling the criteria for established GCSE. Initial treatment was defined as the first given antiepileptic drug (AED), which was not necessarily the first-stage medication. The second-stage medication was defined as first given second-stage medication, mainly intravenous (i.v.) phosphenytoin. Diagnosis of GCSE was made by the EMS or ED physician on clinical grounds or with the aid of Electroencephalogram (EEG) recording. Tertiary hospital referred to HUCH ED at all times. The cessation of GCSE was defined with three separate parameters for the treatment response [28]: BS, clinical seizure freedom, and return of consciousness. Burst-suppression refers to the beginning of the first BS sequence during this SE. Clinical seizure freedom refers to the end of the last clinical convulsion, and return of consciousness refers to the time point, when the patient no longer presented with altered mental status. The length of treatment (anesthesia/Intensive Care Unit (ICU)) was calculated by adding up the total length of all individual anesthesia- / ICU-periods during the GCSE.

Long-term outcome of the patients was defined as mortality at 90 days, 1 year, or during the 1-year follow-up period.

2.6. Statistics

Results are given as number of cases and percentage or median and interquartile range (IQR).

Ninety days and 1-year mortality were analyzed with univariate logistic regression analyses. Survival analyses at 1 year were performed with the Cox proportional hazards regression analysis and the Kaplan–Meier method with the log rank test.

Parameters for multivariate analysis at 1 year were selected based on univariate analyses and clinical relevance. Significant parameters correlating statistically or clinically were excluded from the multivariate models. Parameters selected for multivariate Cox proportional hazards analysis were STESS >4, CBI as an ordinal variable (0–2, 3–6, >6), worse-than-baseline condition at hospital discharge, and diagnostic delay with cutoff at 6 h.

p values <0.05 are considered significant, and two tailed tests were used. Statistical analyses were performed with the SPSS software (version 24.0, IBM Corp., NY, USA).

3. Results

In-hospital mortality was 7.1% in this study. Mortality rate was 14.3% at 90 days and 24.3% at 1 year after GCSE.

In the univariate logistic regression analysis, STESS >4 (ODDS = 7.30, $p = 0.012$), worse-than-baseline condition at hospital discharge (ODDS = 3.5, $p = 0.006$), long delays in attaining seizure freedom (ODDS = 2.2, $p = 0.041$), and long delays in gaining consciousness (ODDS = 3.4, $p = 0.014$) were risk factors for mortality at 90 days. Previously diagnosed epilepsy (ODDS = 0.2, $p = 0.014$) and good condition at hospital discharge evaluated with GOS >3 (ODDS = 0.05, $p = 0.006$) were protective factors regarding mortality at 90 days.

Status Epilepticus Severity Score >4 (ODDS = 5.1, $p = 0.028$), use of vasopressors (ODDS = 8.2, $p = 0.049$), and worse-than-baseline condition at discharge (ODDS = 7.8, $p = 0.010$) were risk factors for mortality at 1 year, whereas GOS >3 at hospital discharge (ODDS = 0.2, $p = 0.005$) was protective.

Complication Burden Index was analyzed with a cutoff point of 3, which proved insignificant for predicting mortality in this study. However, CBI as a continuous variable had slightly better but insignificant results in predicting both 90 days ($p = 0.093$) and 1-year mortality ($p = 0.066$) after GCSE. Delay parameters just not reaching statistical significance in predicting mortality at 90 days were onset-to-diagnosis-time ($p = 0.054$), onset-to-tertiary-hospital time ($p = 0.05$), onset-to-BS time ($p = 0.085$), and length-of-ICU-treatment ($p = 0.063$). At 1 year, length-of-ICU-treatment remained slightly below significant association with mortality ($p = 0.057$).

The results of the comprehensive univariate analysis are presented in Table 3.

The univariate survival analysis with Cox proportional hazards regression analysis at 1 year confirmed the significant findings regarding

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Table 3
The results of the comprehensive univariate analysis.

Variable		All cases	90 days mortality						1 year mortality					
			Dead	Alive		95% CI	95%CI		Dead	Alive		95% CI	95% CI	
		N (%)	N (%)	N (%)	ODDS	Min	Max	p	N (%)	N (%)	ODDS	Min	Max	p
Demographics		70 (100)	10 (14)	60 (86)					17 (24)	53 (76)				
Gender	Male	35 (50)	6 (60)	29 (48)	1.60	0.40	6.30	0.497	10 (59)	25 (47)	1.60	0.50	4.80	0.405
Age	>65	19 (27)	4 (40)	15 (25)	2.00	0.50	8.10	0.330	6 (35)	13 (25)	1.70	0.50	5.40	0.388
Epilepsy	Yes	46 (66)	3 (30)	43 (72)	0.20	0.00	0.70	**0.014**	8 (47)	38 (72)	0.30	0.10	1.00	0.053*
CCI	>2	18 (26)	1 (10)	17 (28)	0.28	0.03	2.39	0.245	3 (18)	15 (28)	0.54	0.14	2.16	0.387
GCSE characteristics														
STESS	>2	35 (50)	7 (70)	28 (47)	2.70	0.60	11.30	0.183	10 (59)	25 (47)	1.60	0.50	4.80	0.405
STESS	>3	19 (27)	4 (40)	15 (25)	2.00	0.50	8.10	0.330	6 (35)	13 (25)	1.70	0.50	5.40	0.388
STESS	>4	9 (13)	4 (40)	5 (8)	7.30	1.50	35.00	**0.012**	5 (29)	4 (8)	5.10	1.20	21.90	**0.028**
Prestatus period	Yes	14 (20)	1 (10)	13 (22)	0.40	0.00	3.50	0.407	2 (12)	12 (23)	0.50	0.10	2.30	0.338
SE onset	Intermittent	25 (36)	4 (40)	21 (35)	1.20	0.30	4.90	0.760	5 (29)	20 (38)	0.70	0.20	2.20	0.534
Refractoriness	SRSE	32 (46)	6 (60)	26 (43)	2.00	0.50	7.70	0.333	9 (53)	23 (42)	1.50	0.50	4.40	0.493
Treatment and complications														
Anesthetic treatment	Only propofol	56 (80)	8 (80)	48 (80)	1.20	0.10	10.80	0.892	14 (82)	42 (79)	2.30	0.30	20.70	0.446
Burst-suppression	Yes	30 (43)	7 (70)	23 (38)	3.80	0.90	16.00	0.074*	9 (53)	21 (40)	1.70	0.60	5.10	0.227
Use of vasopressors	Yes	51 (73)	9 (90)	42 (70)	3.90	0.50	32.70	0.216	16 (94)	35 (66)	8.20	1.00	67.10	**0.049**
Mechanical ventilation	Yes	62 (89)	9 (90)	53 (88)	1.20	0.10	10.80	0.878	16 (94)	46 (87)	2.40	0.30	21.30	0.422
CBI	>3	32 (46)	7 (70)	25 (42)	3.27	0.77	13.88	0.190	9 (53)	23 (43)	1.47	0.49	4.39	0.493
CBI	Continuous variable	70 (100)	10 (100)	60 (100)	1.30	0.96	1.78	0.093*	17 (100)	53 (100)	1.29	0.98	1.70	0.066*
Infections	Yes	61 (87)	10 (100)	51 (85)				0.999	16 (94)	45 (85)	2.80	0.33	24.56	0.342
Outcome at hospital discharge														
GOS	>3	42 (60)	1 (10)	41 (68)	0.050	0.006	0.436	**0.006**	5 (29)	37 (70)	0.18	0.05	0.60	**0.005**
Condition	Worse-than-baseline	41 (59)	10 (100)	31 (52)	3.500	1.600	+inf	**0.006**	15 (88)	26 (49)	7.79	1.62	37.46	**0.010**
Delays		Time h/(IQR)	Time h/(IQR)	Time h/(IQR)					Time h/(IQR)	Time h/(IQR)				
Onset-to-initial-treatment		0.5 (0.8)	0.2 (0.9)	0.5 (0.7)	0.6	0.2	1.9	0.265	0.3 (0.6)	0.5 (0.8)	0.7	0.3	1.5	0.318
Onset-to-diagnosis		1.8 (2.8)	3 (10.8)	1.7 (2.6)	4.3	0.8	156.6	0.054*	2 (5)	1.6 (2.6)	1.9	0.5	12.4	0.26
Onset-to-second-stage-treatment		2.7 (3.4)	4.8 (6.2)	2.6 (2.2)	3.1	0.3	116.1	0.24	3.4 (4.6)	2.6 (2.2)	1.3	0.2	9	0.726
Onset-to-tertiary-hospital		2.4 (2.8)	3.9 (25)	2.3 (2.6)	3.1	0.4	38.5	0.057*	2.4 (3.9)	2.4 (2.6)	1.6	0.3	6.8	0.412
Onset-to-burst-suppression		14.7 (19)	28.5 (32.8)	12.5 (18.3)	9.6	0.4	24,612.3	0.085*	22 (28.7)	14 (19.3)	2.4	0.1	609	0.488
Onset-to-seizure-freedom		5.3 (46.6)	27.7 (50.5)	4.3 (45.3)	2.2	0.9	8.8	**0.041**	8.4 (50.6)	4.5 (43.9)	1.4	0.6	3.5	0.393
Onset-to-consciousness		42.8 (42.8)	59.5 (56.25–89.33**)	36.5 (52.8)	3.4	1.6	12.2	**0.014**	57.9 (68.8)	38 (53.1)	2.2	0.6	12.5	0.226
Length-of-the-anesthesia-treatment		38 (51.2)	39.5 (68.5)	36 (50.7)	3.6	0.9	23.6	0.223	36.9 (66.2)	38 (50.3)	2	0.3	13.8	0.436
Length-of-the-ICU-treatment		58.7 (106.8)	85.3 (112.6)	58.5 (111.4)	3.4	0.9	23.6	0.063*	62.3 (101.8)	58.5 (109.6)	3.1	1	13.6	0.057*

Time (h) Median time in hours. *IQR* Interquartile range. **min-max. Only 3 patients. Statistical significance ($p < 0.05$) is expressed in bold. Statistical trend ($p < 0.1$) is expressed with *.

parameters STESS >4 (HR = 4.1, 95%Confidence Interval (CI) 1.43–11.67, $p = 0.009$), worse-than-baseline condition (HR = 6.2, 95%CI 1.42–27.21, $p = 0.015$), GOS >3 at hospital discharge (HR = 0.2, 95%CI 0.08–0.62, $p = 0.004$), and epilepsy (HR = 0.4, 95%CI 0.14–0.98, $p = 0.044$). Vasopressor use (HR = 6.92, 95%CI 0.92–52.2, $p = 0.061$) and CBI as a continuous variable (HR = 1.2, 95%CI 0.99–1.48, $p = 0.067$) remained below the significance.

Continuous variables i.e., delays in treatment and CBI were tested for cutoffs with Receiver operating characteristic curve (ROC-curve) calculations. In survival analysis, diagnostic delay over 6 h (HR = 3.8, 95%CI 1.21–11.7, $p = 0.022$) and CBI as an ordinal variable (0–2, 3–6, >6) (HR = 2.7, 95%CI 1.12–6.6, $p = 0.027$) were found to be predictive for mortality, as also seen in Kaplan–Meier curves (Figs. 1 and 2). Onset-to-burst-suppression time with a cutoff of 17.5 h (HR = 3.5, 95%CI 0.88–14.2, $p = 0.075$) was not quite statistically significant.

Results of the multivariate survival analysis are presented in Table 4. Status Epilepticus Severity Score >4 (HR = 5.1, $p = 0.007$), CBI (HR = 3.2, $p = 0.025$, ordinal variable), diagnostic delay over 6 h (HR = 7.2, $p = 0.003$), and worse-than-baseline condition at hospital discharge (HR = 5.8, $p = 0.027$) were all independent risk factors for mortality at 1 year.

4. Discussion

This study brings notable additional information to the field of long-term outcome after GCSE by being the first study also investigating the effect of the delays and complications in the treatment on long-term mortality after GCSE.

Although delays are significant predictors of short-term outcome, the effect seems to reduce as time increases after GCSE. Consequently, at 90 days, several delays still have some effect on mortality while at one year, the effect on outcome has nearly been lost. However, diagnostic delay over 6 h remains a strong predictor for mortality. Additionally, poor functional outcome at hospital discharge, high number of complications during treatment period, and severity of GCSE graded with STESS proved to be independently associated with long-term mortality.

All retrospective studies bear a risk of reporting bias. To cover this bias, we used previously developed scores L_{was} and DA to determine the

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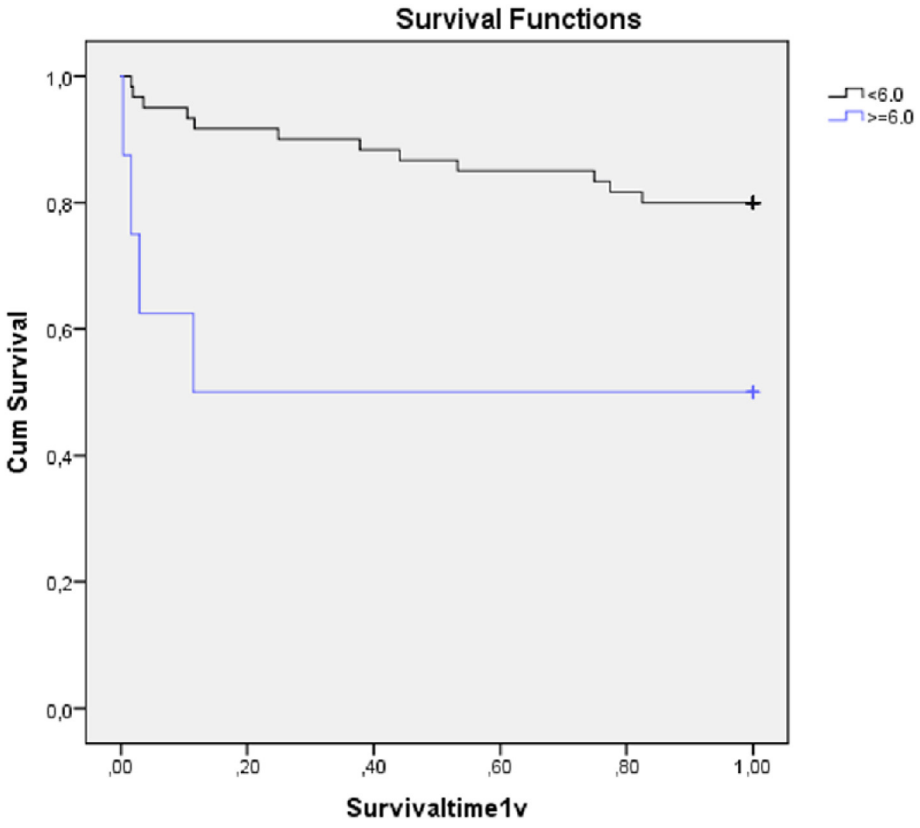

Fig. 1. Kaplan–Meier curve showing the significant difference of effect of the diagnostic delay (<6 h vs. ≥6 h) on mortality during the 1-year follow-up period after GCSE ($p = 0.014$).

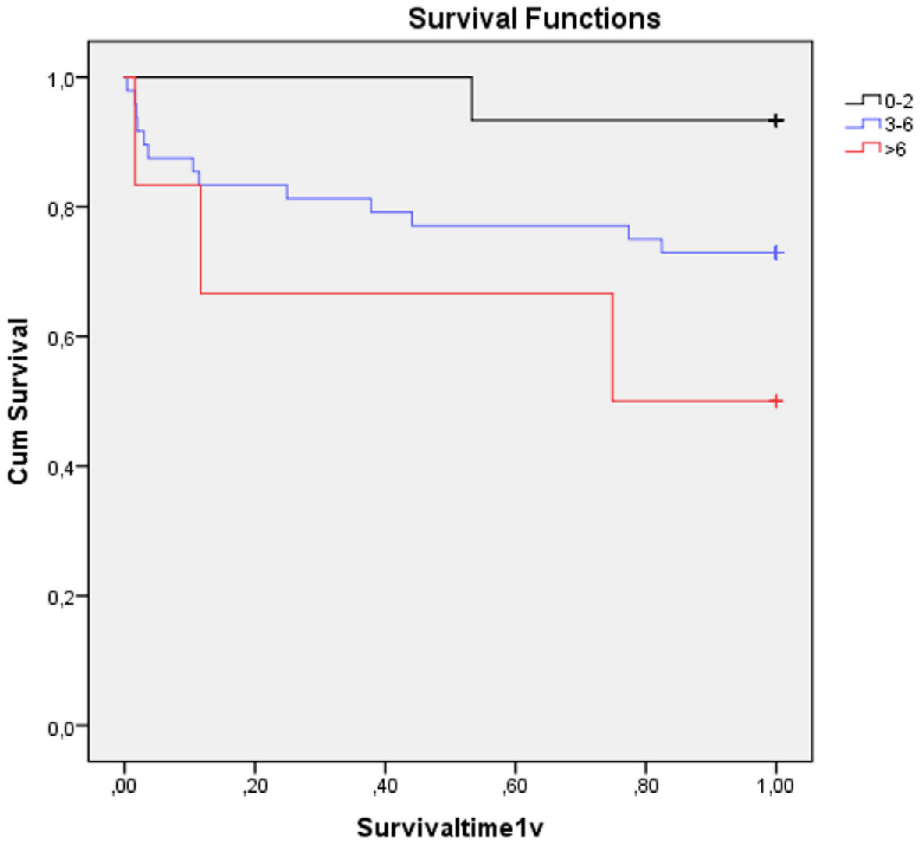

Fig. 2. Kaplan–Meier curve showing the significant difference of the CBI (0–2, 3–6, >6, ordinal variable) on mortality during the 1-year follow-up period after GCSE ($p = 0.029$).

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Table 4
The results of the multivariate survival analysis at 1 year after GCSE.

Variable		HR	95%CI	95% CI	p
			Min	Max	
STESS	>4	5.13	1.57	16.77	0.007
CBI	0–2/3–6/>6	3.19	1.16	8.82	0.025
Onset-to-diagnosis	>6 h	7.19	1.92	26.99	0.003
Condition at discharge	Worse-than-baseline	5.78	1.23	27.24	0.027

accuracy and reliability of the collected time parameters. The Finnish EMS is very punctual in its markings guaranteeing a high level of accuracy, which is highlighted in a good L_{was} and DA throughout the study.

The material in this study is relatively old, and at the time of data collection, the definition of SE was a seizure lasting for at least 30 min, instead of the current definition of 5 min. However, the treatment protocols have not markedly changed during the past 15 years, and therefore, the material is comparable with studies with newer data. Nowadays, EEG recording in the acute phase is readily available in the ED in Helsinki whereas at the time of material collection, acutely registered EEG data were nearly lacking. For this reason, the calculation of EMSE score was not possible in this material.

The sample size is relatively small, which may be seen as the biggest limitation of our study. Nevertheless, it is fairly comparable with the sample sizes in previous studies. According to the patient distribution protocol, patients not independent in ADL functions are treated in regional hospitals and not in HUCH. Therefore, they are not included in this material. The large proportion of patients with RSE and SRSE in this material highlights the tertiary hospital status of HUCH, where the most difficult cases of GCSE are treated in Southern Finland. These factors result in patient selection bias in our study population. However, it may enable us to diminish the effect of overall frailty of patients on long-term prognosis and focus more on the factors related solely to SE. These abovementioned limitations may warrant some precaution in interpreting the results of this study.

4.1. Mortality

Mortality increased from in-hospital mortality up to one year, when about one-fourth of the patients had died. While this seems quite high, it is, in fact, in the lower range of long-term mortality reported in previous studies [6,18–21]. This may partly reflect the overall good premorbid condition in our study population due to patient selection.

4.2. Outcome score variables

In this study, STESS was associated with poor long-term prognosis of GCSE with a score >4. Studies regarding the prognostic value of STESS as an indicator of long-term outcome have been published with opposing results [18,22,24–27]. In one study, all individual components of STESS except "history of previous seizures" seemed to be associated with long-term mortality, but overall STESS with a cutoff of 4 was not associated with survival after discharge [24]. The prognostic value of STESS for long-term outcome is still unclear, but the results of this present study are indicative of its usefulness in predicting long-term mortality, which possibly broadens the usability of the score and could serve as a basis for the future development of new outcome scores used for prediction of long-term outcome.

A few studies have investigated the role of EMSE score in predicting long-term outcome of SE with promising results [26,27]. In a recent study by Møller et al., epidemiology-based mortality score in status epilepticus, etiology-age-comorbidity-EEG (EMSE-EACE) was significantly associated with mortality after discharge, but in the same patients, STESS ≥3 reached only borderline significance and STESS ≥4 was not statistically significant [26]. Because of the lacking EEG recordings on hospital admission for most of the cohort, EMSE score could not be determined in this study.

The protective value of previous epilepsy on mortality seen in this study possibly reflects the worse prognosis of severe symptomatic causes resulting in SE. This finding is in line with other studies, where acute symptomatic, progressive symptomatic, and potentially fatal etiologies have been seen to predict long-term mortality [18,23,27,30]. Although Kantanen et al. could not confirm the positive predictive value of earlier epilepsy at 1 year after SE, they found that the poor outcome in patients with preexisting epilepsy was related to remote symptomatic etiology or to a progressive syndrome, indicating that also, patients with epilepsy are at risk for etiologies with unfavorable outcome [24].

Older age has been associated with worse long-term outcome [6,18,30], but individual patients up to the age of 79 years have been reported to recover functionally after RSE [24]. In our study, we could not confirm the significance of age as an individual parameter predicting long-term mortality. This finding may at least partly be explained by the patient distribution protocol in HUCH area directing patients dependent in ADL functions to regional hospitals. Since dependence of aid due to illness and frailty is more common in the elderly population, the patient selection might influence our results regarding the prognostic value of age on mortality. The effect of the premorbid condition on the long-term prognosis has been reported earlier [6]. Because of the patient distribution protocol in HUCH, only a clear minority of patients in our material had a premorbid GOS of <4, thus, the effect on mortality could not be analyzed.

4.3. Functional outcome at hospital discharge

Only one study has previously reported the significance of condition at hospital discharge on long-term mortality, where modified Rankin Scale (mRS) >2 was the predictor [31]. In our study, the condition at discharge was evaluated categorically with GOS and comparatively to baseline condition prior SE. Poor condition in any of these measures was a significant predictor of mortality at 1 year after GCSE. Since associations between delays in the treatment and functional outcome at discharge have been reported [11], this new finding highlights even more the importance of how effectively patients with SE should be managed in the early phases of the SE.

4.4. Duration of SE and delays in the treatment

Long duration of SE is a reported risk factor for long-term mortality [18,22,23]. Definition of SE duration alternates between SE studies, since the exact endpoint of SE is conceptually problematic and used definitions contain variability [32,33]. We used stepwise definition for the end of GCSE as described in Section 2.5 and found that the longer the duration from SE onset to seizure-freedom and to return of consciousness, the higher the mortality rate at three months after GCSE. A previous study of this same cohort showed that delay in return of consciousness was related to poor outcome at hospital discharge and in-hospital mortality [11]. Interestingly, predictive association of this delay with mortality found at discharge and at 90 days was lost at 1-year follow-up.

Delays in the treatment of SE are associated with short-term outcome among both pediatric and adult patients [11,12]. The need to minimize delays and optimize every component in the treatment chain has been shown to be an important determinant of outcome [11]. None of the previous studies have focused on the effect of delays on long-term mortality. Although most of the delays in treatment in our study did not reach significance, several delays showed trend-like effect on mortality at 90 days. Nonetheless, we found that if the delay in diagnosing GCSE exceeded 6 h, it had a significant effect on long-term survival. The same phenomenon has been reported with short-term outcome, where diagnostic delay over 2.4 h was predictive [11]. These findings elucidate the importance of early diagnosis of SE. Electroencephalogram (EEG) is not available in EMS, and 24/7 EEG-recording possibilities are lacking in most of the EDs. Therefore, the diagnosis of SE in the early

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phases of the treatment is based on clinical judgment. Recently published ADAN scale (Abnormal speech, eye deviation, automatism, number of seizures) might bring some help for the clinical evaluation [34]; however, substantial effort should be accomplished to improve the diagnostic facilities.

4.5. Refractoriness and ICU treatment

Superrefractoriness in SE has been reported to be an independent risk factor for long-term mortality in a material based on ICU-treated SE cases [6]. This relation between superrefractoriness and long-term mortality could not be confirmed in this study, which might be partly explained by the different study designs.

Refractory cases mostly require ICU treatment, which might be prolonged especially in SRSE cases. Prolonged hospital and ICU treatment periods are associated with poor outcome and mortality at hospital discharge [4,10]. On the contrary, a previous study concluded that the length of ICU treatment did not differ between patients with good and poor long-term outcomes [24]. This finding is partially in line with our results, where the length of ICU treatment was not an independent predictor of long-term mortality, although a trend-like association was found.

In earlier studies, intravenous anesthetic drug (IVAD) treatment itself has not been associated with short-term mortality [35] nor the long-term mortality after SE [22]. These findings are supported by our results. We could neither find difference between the use of propofol only compared with the use of multiple anesthetics. Long anesthesia time has been associated with poor short-term outcome [11,36], however, similar association was not found in predicting long-term mortality in this present study.

Treatment complications increase as the length of the SE period increases [37], and complications might be one of the reasons for poor outcome in long SE treatment episodes [4]. Intensive Care Unit (ICU) and IVAD treatments are risk factors for infections, hypotension, need for intubation and mechanical ventilation, and other systemic complications [3,38]. Vasopressor use, infections, and mechanical ventilation have been associated with short-term outcome in previous publications [10,36,39]. Most of these factors do not increase long-term mortality [22], however, sepsis and severity of organ dysfunction (Sequential Organ Failure Assessment Score (SOFA score)) are associated with poor long-term outcome [6,22]. In this study, vasopressor use was associated with mortality at one year. Furthermore, our study showed that an increasing total number of complications was independently associated with long-term mortality. This finding increases the importance of high quality in intensive care but also underlines the importance of measures taken to prevent nonrefractory SE evolving to RSE.

5. Conclusion

Results of this study show that the severity of SE, number of treatment complications, diagnostic delay over 6 h, and poor functional condition at hospital discharge have significant effect on long-term prognosis of GCSE. These findings demand for aggressive treatment of SE aiming for early seizure termination, shorter treatment periods, and fewer complications during the treatment. Our study underlines the importance of rapid diagnostics of SE also on long-term survival, highlighting the need for EMS personnel education, on-call EEG availability and development, and implementation of SE recognition algorithms.

Interestingly, our study showed that prognostic factors for mortality changed over the 1-year follow-up period, from 90 days to 1 year, thus, it is presumable that the predictive factors keep on changing as time passes by. The knowledge of mortality and causes of death during a longer follow-up period than 1 year is limited, which claims for further studies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.07.012.

Declaration of Competing Interest

None.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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