Clinical Outcomes and Risk Factors for Mortality in Status Epilepticus Patients

Abstract

Background: The outcome and risk factors for mortality in status epilepticus (SE) largely varies depending on clinical characteristics, and assessment tools in SE. The aim of this study is to determine risk factors for short-term mortality and outcomes in SE.

Methods: From January 2014 to August 2021, we performed a retrospective study in SE patients who were admitted at Ramathibodi hospital. All adults (≥ 18 years) with the diagnosis of SE according to the International League Against Epilepsy (ILAE) definition and classification of SE were included. We excluded SE patients with normal awareness, and posthypoxic SE. Univariate and multivariate logistic regression were used to identify risk factors.

Results: A total of 124 patients were included (female/male, 73/51, mean age (SD) of 61.29 (21.52)). Thirty-four patients (27.42%) died within 30 days. The median hospital stay (IQR) was 20 (9, 42) days. By using univariate analysis, elderly, therapy delay >60 minutes, baseline mRS ≥4, high mSTESS, EEG status, heart disease, liver disease, and infection were significant risk factors. The history of seizure was preventive factor. Multivariate analysis revealed that the time to treatment (OR [95%CI], 2.85 [1.15, 7.05]), history of seizure (0.24 [0.06, 0.89]), heart disease (3.67 [1.24, 10.87]), and liver disease (31.48 [2.46, 402.65) were significant factors predicting SE mortality.

Conclusions: Therapy delay with time to treatment more than 60 minutes, heart disease, liver disease, and infection were significant risk factors for short-term mortality in SE. The history of seizure was a preventive factor for SE mortality.

Keywords: Status epilepticus, Risk factor, Mortality, Seizure

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Introduction

Status epilepticus (SE) is a time-sensitive emergency condition which is associated with high short-term mortality. Over the past decades, major advances in SE have been notably observed. There are numerous factors which predict outcome in SE such as age, type of seizure, duration of seizure, pre-existing comorbidities, and de novo seizure.[1]

The definition and classification of SE by the International League Against Epilepsy (ILAE) Task Force[2], the American Clinical Neurophysiology Society Critical Care electroencephalogram (EEG) Terminology, Salzburg criteria for non-convulsive SE (NCSE), modified Rankin scale and Status Epilepticus Severity Score (mSTESS) have been proposed to guide clinicians in SE management.

Furthermore, there have been clear advances in the understanding of the pathophysiologic mechanisms of SE, which have led to more effective treatment strategies. To best of our knowledge, the application of these SE instruments in Thais have been limited because they are recently developed, not widely used, and required specialized training.

Aforementioned, the usage of these SE instruments have been applied in our research. The aim of this study is to determine the clinical outcomes and risk factors for mortality in SE patients.

Objective

The primary objective of this study is to identify the risk factors for mortality within 30 days in SE patients. The secondary objective is to identify the relationships between mortality and patient-related clinical factors including SE definition and classification of SE based on the 2015 ILAE criteria,

EEG findings based on the American Clinical Neurophysiology Society Critical Care EEG Terminology, modified Rankin scale and Status Epilepticus Severity Score (mSTESS) in SE patients.

Materials and Methods

Study design

This study was a retrospective observational study of patients who was hospitalized due to SE at Ramathibodi hospital between January 2014 and August 2021. The electronic medical records and continuous EEG(CEEG) monitoring database of the SE patients were retrospectively reviewed.

The study was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (Approval Certificate ID: MURA 2022/674). The study was carried out in accordance with the Declaration of Helsinki and the Conference on Harmonization Guidelines for Good Clinical Practice and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines.

Participants

Inclusion criteria

All adults (≥ 18 years) with the diagnosis of SE according to the International League Against Epilepsy (ILAE) definition and classification of SE were included.

Exclusion criteria

We excluded SE patients with normal awareness, and posthypoxic SE.

Definition of terms

The definition and classification of SE by the International League Against Epilepsy (ILAE)Task

Force and Salzburg criteria for NCSE were used in this study.[2]

The Modified Rankin Scale (mRS) is a clinician-reported measure of global disability. There are 7 scores ranging from 0 to 7. Symptom-free functional level (mRS score 0), non-significant disability (mRS score 1), slight disability (mRS score 2), moderate disability (mRS score 3), moderately severe disability (mRS score 4), severe disability (mRS score 4), and death (mRS score 6)[4]

Status epilepticus severity score (STESS) is a prognostic score based on four outcome predictors: age (<65 years=0; ≥65 years=2), history of previous seizures (yes=0; no=1), worst seizure type (simple focal, complex focal, absence, and myoclonic seizures=0; generalized convulsive=1; NCSE in coma/subtle SE=2), and extent of impairment of consciousness (alert or somnolent/confused=0; stuporous or comatose=1)[3]

The Modified Rankin Scale (mRS) plus Status epilepticus severity score (STESS) is defined as mSTESS in this study.

The short-term mortality rate is defined as the death within 30 days after hospitalization with SE.

Statistical analysis

Sample size

No sample size was calculated. All patients who met eligibility criteria were included in analysis. A good general rule of thumb for factor analysis[5], 300 cases or the more lenient 50 participants per factor, was expected.

Statistical Analysis

Statistical analyses were performed using STATA Statistics for Windows, Version 14.0 (Stata Corp LLC, Texas, USA). For continuous variables, mean with standard deviation (SD) or median with interquartile range (IQR) were used for data presentation as appropriate. Frequencies with percentages were used to describe for categorical data.

Two-sample t test or two-sample Wilcoxon rank-sum (Mann-Whitney) test were used to determine the differences of continuous parameters among the alive and death patients. For categorical data, Chi-square or Fisher exact test was used to test the differences among groups. Univariate and multivariate logistic regression (backward stepwise method) were used to identify the mortality risk factors. All variables with a *p*-value ≤ 0.10 in the univariate analysis were included in multivariate analyses with backward stepwise elimination in order to identify the significant factors related to the deaths. Odds ratios, with corresponding 95% CI, were calculated to represent the magnitude of association between death and risk factors. The analysis was performed using STATA version 14.0 and *p*-value of <0.005 was considered statistically significant.

Results

Patients' demographics and characteristics

A total of 124 SE patients (73 (58.87%) females and 51 (41.13%) male) met the criteria and were reviewed. Of 124, 104 patients (83.87%) were admitted in ICU. There were 31 patients (25%) who underwent for tracheostomy insertion. Thirty-four patients died within 30 days (27.41%, 95%CI 19.79% to 36.15%). Median mRS at baseline and discharge (IQR) was 2 (0-5) and 5 (3, 5.5), respectively. Median time to treatment (IQR) was 30 minutes. Median length of stays (IQR) were 20 days (42 days).

Approximately one third of SE patients (30%) had therapy delay more than 60 minutes. Half of the patients were stuporous or comatose patients (69/124, 55.65%). Mean STESS and mSTESS scores (SD) were 3.27 (1.43) and 5.54 (2.80), respectively. Approximately one third of the patients had remote symptomatic seizure. The highest etiology of seizure was stroke (32%). Hypertension was the highest pre-existing comorbidities of the patients (54.84%), followed by dyslipidemia(37.9%), diabetes(32.26%), respectively. Generalized convulsive SE was the highest SE semiology (61.29%), followed by focal onset evolving into bilateral convulsive SE, NCSE with coma and NCSE without coma, respectively. (Table 1)

Factor related to death in 30 days

Univariate analysis showed that higher age at admission (OR [95%CI], 1.02 [1.00, 1.04]), time to treatment > 60 minutes (3.28 (1.42, 7.56), baseline mRS ≥ 4 (2.41 [1.07, 5.38]), mSTESS score (1.18 [1.01, 1.36]), EEG status (3.88 [1.31, 11.50]), heart disease (3.75 [1.36, 10.28]), liver disease (11.86 [1.27, 110.36]), and hospital acquired infection (3.17 [1.33, 7.55]) were significantly associated with high risk of mortality. Generalized convulsive SE (0.37 [0.16, 0.84]), and history of seizure (0.34 [0.14, 0.84]) were not associated with high risk of mortality. There was no association with sex, consciousness, STESS score, acute/remote etiologies, diabetes, hypertension, dyslipidemia, and dementia. (Table 2).

Backward stepwise logistic regression begun with full model included the variables with p-value < 0.10 from univariate analysis, i.e., age at admission, baseline mRS ≥ 4, time to treatment >60 minutes, stuporous or comatose, generalized convulsive SE, history of seizure, mSTESS score, diabetes, heart disease, ESRD, liver disease, malignancy, and infection. But, EEG status was not included due to unavailability of CEEG data in approximately half of SE patients. At the full model, there were 2 factors significantly associated with the death, i.e., time to treatment (OR [95% CI], 2.82 [1.01, 7.8], $p= 0.046$), and history of seizure (0.20 [0.049, 0.88], $p= 0.033$). The best model which includes only important variables from backward stepwise logistic regression with removing variable with p-value ≥ 0.05, revealed that time to treatment > 60 minutes (OR [95%CI], 2.85 [1.15-7.05], $p= 0.016$), history of seizure (0.24 [0.06, 0.89], $p= 0.034$), heart disease (3.67 [1.24, 10.87], $p= 0.019$), and liver disease (31.48 [2.46, 402.65], $p= 0.019$) were the important factors predicting SE mortality.

Table 1 Baseline characteristic and demographic data

	All	Alive N= 90	Dead N= 34	p
Male, n (%)				
Female	73 (58.87)	53 (58.89)	20 (58.82)	0.995a
Male	51 (41.13)	37 (41.11)	14 (41.18)	
mRS at baseline, median (IQR)	2 (0, 5)	2 (0, 5)	4 (0, 5)	0.118[d]
mRS at baseline				
< 4	74 (59.68)	59 (65.56)	15 (44.12)	0.030*[c]
≥ 4	50 (40.32)	31 (34.44)	19 (55.88)	
mRS at discharge, median (IQR)	5 (3, 5.5)	5 (1, 5)	6 (6, 6)	N/A

Table 1 Baseline characteristic and demographic data (cont.)

	All	Alive N= 90	Dead N= 34	p
Axis I: Semiology				
Generalized convulsive SE	76 (61.29)	61 (67.78)	15 (44.12)	0.016[a]*
Focal onset evolving into bilateral convulsive SE	29 (23.39)	18 (20.00)	11 (32.35)	0.147[a]
Non convulsive SE with coma	10 (8.06)	5 (5.56)	5 (5.56)	0.135[b]
Non convulsive SE without coma	9 (7.26)	6 (6.67)	3 (8.82)	0.705[b]
Axis II: Etiology, n (%)				
Acute	82 (66.13)	58 (64.44)	24 (70.59)	0.519[a]
Remote	42 (33.87)	32 (35.56)	10 (29.41)	
Stroke	32 (25.81)	22 (24.44)	10 (29.4)	0.573[a]
Autoimmune encephalitis	7 (5.65)	6 (6.67)	1 (2.94)	0.672[b]
CNS infection	11 (8.87)	8 (8.89)	3 (8.82)	1.000[b]
Drug intoxication or withdrawal	2 (1.61)	0	2 (2.22)	1.000[b]
Traumatic brain injury	14 (11.29)	10 (11.11)	4 (11.76)	1.000[b]
Poor compliance of antiepileptic drug	9 (7.26)	7 (7.78)	2 (5.88)	1.000[b]
Brain tumor	9 (7.26)	5 (5.56)	4 (11.76)	0.256[b]
Remote structural brain lesion	13 (10.48)	12 (13.33)	1 (2.94)	0.111[b]
Axis III: EEG correlates (n=68)				
No epileptiform discharge	30 (44.12)	23 (52.27)	7 (29.17)	0.067[a]
EEG status	21 (30.88)	9 (20.45)	12 (50.00)	0.012[a]*
Ictal-interictal continuum (IIC)	17 (25.00)	12 (27.27)	5 (20.83)	0.558[a]
Axis IV: Age at admission (year), mean (SD), (min, max)	61.29 (21.52) 17, 95	58.51 (22.52) 17, 95	68.67 (16.75) 33, 91	0.007[c]
Stuporous or comatose				
Yes	55 (44.35)	44 (48.89)	11 (32.35)	0.098[a]
No	69 (55.65)	46 (51.11)	23 (67.65)	
History of seizure	39 (31.45)	33 (36.67)	6 (17.65)	0.042*
STESS score	3.27 (1.43)	3.18 (1.42)	3.5 (1.46)	0.291
mSTESS score	5.54 (2.80)	5.2 (2.75)	6.47 (2.78)	0.026[c]*
Medical history				
Hypertension	68 (54.84)	46 (51.11)	22 (64.71)	0.175[a]
Diabetes	40 (32.26)	25 (27.78)	15 (44.12)	0.082[a]
Dyslipidemia	47 (37.90)	31 (34.44)	16 (47.06)	0.196[a]
Stroke	36 (29.03)	24 (26.67)	12 (26.67)	0.345[a]
Heart disease	19 (15.32)	9 (10.00)	10 (29.41)	0.007[a]*
Dementia	13 (10.48)	10 (11.11)	3 (8.82)	1.000[b]
ESRD	26 (20.97)	15 (16.67)	11 (32.35)	0.056[a]
Liver disease	5 (4.03)	1 (1.11)	4 (11.76)	0.020[b]*
Malignancy	24 (19.35)	14 (15.56)	10 (29.41)	0.081[a]
Infection				
No	57 (45.97)	48 (53.33)	9 (26.47)	0.007[a]*
Yes	67 (54.03)	42 (46.67)	25 (73.53)	
Time to treatment (mins), median (IQR)(n=98)	30 (5, 120)	30 (5, 90)	90 (7.5, 420)	0.074[d]
Time to treatment				
≤ 60 mins	66 (53.23)	55 (61.11)	11 (32.35)	0.004[a]
> 60 mins	58 (46.77)	35 (38.89)	23 (67.65)	
Tracheostomy insertion	31 (25.00)	26 (28.89)	5 (14.71)	0.104[a]
ICU admission	104 (83.87)	72 (75.5)	32 (28.5)	0.057[a]
Length of stay (days), median (IQR)	20 (9, 42)	19 (9, 42)	21 (10, 33)	0.958[d]

MRS, Modified Rankin Scale for Neurologic Disability, NCSE, Non-convulsive status epilepticus
*Significant (p < 0.05), [a] Chi-square, [b] Fisher's exact, [c] Two-sample t test, [d] Two-sample Wilcoxon rank-sum (Mann-Whitney) test

Table 2 Factors associated with death in 30 days (logistic regression)

		N	Death N (%)	Univariate Logistic regression		Multivariate[b] logistic regression (n=98)	
				OR (95% CI)	P	OR (95% CI)	P
Age at admission (mean (SD),		124	34 (27.41)	1.02 (1.00, 1.04)	0.022*		0.374
Male, n (%)	Female	73	20 (27.40)	Ref	0.995		
	Male	51	14 (27.45)	1.00 (0.44, 2.23)			
mRS at baseline, n (%)	< 4	74	15 (20.27)	Ref	0.032*		0.134
	≥ 4	50	19 (38.00)	2.41 (1.07, 5.38)			
Time to treatment	≤ 60 mins	66	11 (16.67)	Ref	0.005*	Ref	0.023*
	> 60 mins	58	23 (39.66)	3.28 (1.42, 7.56)		2.85 (1.15, 7.05)	
Stuporous or comatose	No	55	11 (20.00)	Ref	0.101		0.327
	Yes	69	23 (67.65)	2.00 (0.87, 4.58)			
Semiology					0.018*		0.955
Generalized-convulsive	No	48	19 (39.58)	Ref			
	Yes	76	15 (19.74)	0.37 (0.16, 0.84)			
History of seizure	No	85	28 (32.94)	Ref	0.047*	Ref	0.034*
	Yes	39	6 (15.38)	0.37 (0.13, 0.98)		0.24 (0.06, 0.89)	
STESS score		124	34 (27.41)	1.16 (0.88, 1.54)	0.281		
mSTESS score		124	34 (27.41)	1.18 (1.01, 1.36)	0.027*		0.637
EEG status	No	47	12 (25.53)	Ref	0.014*[a]		
	Yes	21	12 (57.14)	3.88 (1.31, 11.50)			
Etiology							
Etiology	Acute	82	24 (29.27)	Ref	0.520		
	Remote	42	10 (23.81)	0.75 (0.32, 1.77)			
Stroke	No	92	24 (26.09)	Ref	0.573		
	Yes	32	10 (31.25)	1.28 (0.53, 3.10)			
Autoimmune encephalitis	No	117	33 (28.21)	Ref	0.435		
	Yes	7	1 (14.29)	0.42 (0.04, 3.66)			
CNS infection	No	113	31 (27.43)	Ref	0.991		
	Yes	11	3 (27.27)	0.99 (0.24, 3.98)			
Traumatic brain injury	No	110	30 (27.27)	Ref	0.918		
	Yes	14	4 (28.57)	1.06 (0.31, 3.66)			
Poor compliance antiepileptic drug							
	No	115	32 (27.83)	Ref	0.718		
	Yes	9	2 (22.22)	0.74 (0.14, 3.75)			
Brain tumor	No	115	30 (26.09)	Ref	0.245		
	Yes	9	4 (44.44)	2.26 (0.57, 9.00)			
Remote structural brain lesion							
	No	111	33 (29.73)	Ref	0.126		
	Yes	13	1 (7.69)	0.19 (0.02, 1.57)			

Table 2 Factors associated with death in 30 days (logistic regression) (cont.)

		N	Death N (%)	Univariate Logistic regression		Multivariate[b] logistic regression (n=98)	
				OR (95% CI)	P	OR (95% CI)	P
Medical history							
Hypertension	No	44	12 (21.43)	Ref	0.177		
	Yes	46	22 (32.35)	1.75 (0.77, 3.96)			
Diabetes	No	84	19 (22.62)	Ref	0.085		0.557
	Yes	40	15 (37.50)	2.05 (0.90, 4.65)			
Dyslipidemia	No	77	18 (23.38)	Ref	0.199		
	Yes	47	16 (34.04)	1.69 (0.75, 3.77)			
stroke	No	88	22 (25.00)	Ref	0.347		
	Yes	36	12 (33.33)	1.5 (0.64, 3.48)			
Heart disease	No	105	24 (22.86)	Ref	0.010*	Ref	0.019*
	Yes	19	10 (52.63)	3.75 (1.36, 10.28)		3.67 (1.24, 10.87)	
Dementia	No	111	31 (27.93)	Ref	0.711		
	Yes	13	3 (23.08)	0.77 (0.19, 3.00)			
ESRD	No	98	23 (23.47)	Ref	0.060		0.409
	Yes	26	11 (42.31)	2.39 (0.96, 5.92)			
Liver disease	No	119	30 (25.21)	Ref	0.030*	Ref	0.008*
	Yes	5	4 (80.00)	11.86 (1.27, 110.36)		31.48 (2.46, 402.65)	
Malignancy	No	100	24 (24.00)	Ref	0.086		0.056
	Yes	24	10 (41.67)	2.26 (0.89, 5.74)			
Infection	No	57	9 (15.79)	Ref	0.009*		0.101
	Yes	67	25 (37.31)	3.17 (1.33, 7.55)			
Tracheostomy insertion	No	93	29 (31.18)	Ref	0.111		
	Yes	31	5 (16.13)	0.42 (0.14, 1.21)			

Variable with p-value < 0.10 were selected into multivariate logistic regression model with backward stepwise elimination.

a. Not included in multivariate analysis due to no EEG results in approximately half of SE patients.

Discussion

In our study, the SE mortality rate was 27.41% (95% CI, 19.79%-36.15%) which was slightly higher than the previous studies. A meta-analysis showed that pooled case fatality rate was 14.9% (95% CI: 11.7-18.7).[6] A large epidemiology of SE in Richmond, Virginia, U.S.A. reported the overall mortality was 22%.[7] A retrospective cohort study of Huang TH, et.al. in 59 patients, the SE patients classified as non-survivors was 6 patients (10.16%).[8] The overall SE mortality rate in our setting seem to

be higher that other studies[6-8]. The reason is possibly explained by a difference in clinical characteristics of SE patients. Age is a well-known risk factor for mortality of SE. We found that the mortality rate in the elderly patients (n=63) was 28.57% (95% CI, 17.89-41.34) which was comparable to the mortality rate of elderly in a meta-analysis of SE (24.9%, 95% CI: 15.5-37.5).[6]

By using univariate analysis, our study showed that higher age at admission, time to treatment > 60 minutes, baseline mRS ≥ 4, mSTESS score, EEG status, heart disease, liver disease, and

infection were risk factors for SE mortality. Generalized conclusive seizure, and history of seizure were significantly associated low risk of mortality. Multivariate analysis showed that 3 variables, i.e., time to treatment > 60 minutes, heart disease, and liver disease were significant associated with SE mortality. The history of seizure was the significant protective factor.

A retrospective cohort study of Huang TH, et.al. in 59 patients, revealed that effects of the variables of age, sex, underlying disease(s), and type(s) of antiepileptic drug (AED) use showed no significant different between the survivor and non-survivor groups.[8] In term of sex, our result was similar to this previous study.

For STESS scale, the study of Huang TH, et.al. also reported that the STESS scale showed no significant differences (p = 0.117) between the survivors and the non-survivors. From Huang TH, et.al, reported that mSTESS with a cutoff point of ≥ 4 was not significant variable to predict mortality (sensitivity = 50%, specificity = 56.6%, *p*=0.543).[8] Study of González-Cuevas M, et al comparing the accuracy of STESS and mSTESS reported that mSTESS > 4 established an overall accuracy of 81.8% for predicting mortality, which was considerably higher than the overall accuracy of STESS ≥ 3 (59.6%).[9] In our study, STESS was not the predictive factor of mortality while mSTESS was a significant factor in univariate analysis. We further explored the best cut-off point of mSTESS from our data. The best cut-off point was 7. We used 7 as the cut-off point for mSTESS, and found that mSTESS still had not been the factor for prediction of SE-related mortality in multivariate analysis.

From this present study, multivariate analysis the history of seizure was significantly associated low risk of mortality. In other words, the patients with the first episode of SE had higher mortality 15.38 [5.86-30.52] than those who previously had seizures in the past 32.94 [23.12, 43.98]). A previous study of DeLorenzo R.J., et.al reported that the mortality rate in adults presenting with a first episode of generalized convulsive status epilepticus (GCSE) was as high as 16 to 20%. Therapy delay in SE was the significant risk factor for SE mortality in this study. Our result was consistent from the previous study.[10]

Limitations

The limitations of this study include its retrospective design, the relatively small sample size, and a single site cohort study. Thus, our results may not be readily generalized to populations. Continuous electroencephalography monitoring was not able to perform in all participants due to unavailability of EEG machine and patient's medical conditions.

Future application

Achieving seizure control within the first hour after SE onset is a significant determinant of outcome. Importantly, our study provides relevant information on quality improvement in SE management, and risk factors for in-hospital mortality of SE in Thais. Our data provides useful information for creating effective treatment strategies in SE. All SE patients should be admitted in the intensive care unit to minimize the SE-related complications and mortality.

Conclusion

Therapy delay with time to treatment more than 60 minutes, heart disease, liver disease, and infection were significant risk factors for short-term mortality in SE. The history of seizure was a preventive factor for SE mortality.

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Author disclosure statement

No competing financial interests exist.

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