Salzburg consensus criteria are associated with long-term outcome after non-convulsive status epilepticus

Olav S. Monsson a,b, #, Lars E. Roberg a,b, #, Joanna Gesche a,b, Christoph P. Beier a,b, Thomas Kroigård a,b,*

a Research Unit for Neurology, Odense University Hospital, Odense, Denmark
b University of Southern Denmark, Odense, Denmark

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ABSTRACT
Purpose: To investigate differences in long-term survival and short-term neurological deficits in adult patients fulfilling either sub-criterion of the Salzburg Consensus Criteria (SC) for non-convulsive status epilepticus (NCSE).

Methods: We retrospectively identified a cohort of patients with first-time NCSE epilepticus at Odense University Hospital from 2014 to 2017. Results of electroencephalograms at admission were dichotomized according to the SC (more than 25 epileptiform discharges/10 s was defined as the fast criterion), and groups were compared statistically through survival analysis and in a logistic regression model adjusting for established prognostic determinants in status epilepticus. Secondary outcomes were the associations between SC and neurological deficits at discharge.

Results: One-hundred and six patients fulfilled the SC and were included in the main analysis. In addition, 27 patients had possible NCSE. The fast criterion was significantly associated with decreased mortality 2 years following NCSE (OR 0.31, 95% CI 0.11–0.85, p = 0.039) in a logistic regression analysis after correction for age, etiology, semiology and comorbidity. None of the individual subcomponents of the slow criterion could explain the difference in survival in an exploratory analysis. Functional outcome did not differ between patients fulfilling fast and slow criteria. Patients with a clinical diagnosis of NCSE not fulfilling the SC more often had non-refractory NCSE and a more favorable functional outcome.

Conclusion: The fast diagnostic criterion for NCSE was identified as a new, independent variable associated with long-term survival after NCSE. The results may allow prognostication in patients with NCSE at the time of diagnosis, which could guide decision-making in the clinical setting.

Introduction
Status- epilepticus (SE) is a common neurological emergency associated with considerable morbidity and mortality, especially in its convulsive form [1,2]. The mortality and degree of neuronal damage resulting from its non-convulsive manifestation are thought to be less severe, but the evidence is conflicting [3]. Further, non-convulsive SE (NCSE) is very a heterogeneous condition covering both patients with subtle SE as a late form of convulsive generalized SE and other forms such as focal status. Diagnosis is confirmed by electroencephalography (EEG). The Salzburg Consensus Criteria (SC) [4,5] have been developed to increase diagnostic accuracy. According to these criteria, NCSE is diagnosed in patients with a clinical suspicion of NCSE and either epileptiform discharges (EDs) with a frequency of more than 25/10 s or EDs or rhythmic activity with a frequency of less than 25/10 s combined with other clinical or electroencephalographic features.

A recent study demonstrated a high long-term mortality of more than 50% after a median follow-up of 39 months in a cohort with first-time SE [6] including patients with NCSE. Current prognostic scoring systems, the Epidemiology-based Mortality Score in Status Epilepticus (EMSE) and the Status Epilepticus Severity Score (STESS), [7–9] correlate well with short-term outcomes. Studies investigating the long-term

# These authors contributed equally.
* Corresponding author at: Research Unit for Neurology, Odense University Hospital, Odense, Denmark; University of Southern Denmark, Odense, Denmark, J. B. Winsløws Vej 4, 5000 Odense C, Denmark.
E-mail address: thomas.kroigard@rsyd.dk (T. Kroigård).
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performance of these scores, however, found only intermediary predictive power [10–12]. Accurate prediction of long-term outcome therefore requires identification of new prognostic determinants.

The aim of this retrospective cohort study was to investigate the prognostic value of SC sub-criteria for NCSE in adult patients with first-time NCSE.

We hypothesized that higher frequencies of epileptic discharges, as defined by the SC, would imply an increase in metabolic demands on brain tissue and correlate with subsequent neuronal damage and long-term mortality.

The primary objective was to determine whether fulfillment of the “fast” diagnostic criterion for NCSE (EDs with a frequency > 25/10 s) as opposed to the “slow” criterion differed with respect to long-term survival through survival analysis, and to quantify this association in a multivariate logistic regression model. The secondary objective was to evaluate if neurological deficits and decline in functional independence in activities of daily living at discharge was different between the two groups.

Methods

We performed a retrospective cohort study of adult patients with first-time NCSE from 2014 to 2017 in the region of Southern Denmark at the Department of Neurology at Odense University Hospital (OUH). Data presentation is compliant with the STROBE recommendations [13].

Population

Inclusion

Patients examined between 2014 and 2017 were retrospectively identified through ICD-10 codes (G41.X) from the hospital diagnostic code registry and referrals for acute EEG to the Department of Clinical Neurophysiology due to suspicion of NCSE. Patients with NCSE in 2014 had been included in previously published studies [6,14].

NCSE was defined as a seizure lasting longer than its temporal threshold for treatment initiation (10 min in conjunction with continuous or near-continuous ictal activity on EEG) [15]. NCSE was defined as status epilepticus without prominent motor symptoms. Minor motor phenomena could be present, e.g. in patients with “subtle status” following convulsive SE (SE with prominent motor symptoms). All adult patients (>18 years) with NCSE were eligible.

Exclusion

Patients with anoxic brain damage due to cardiorespiratory arrest, previous episode(s) of SE, without Danish residence (lacking Danish personal identification number), incorrect diagnosis of SE, EEG of technically insufficient quality or incomplete descriptions of the SE episode, were excluded.

Electroencephalographic analysis

Patients diagnosed with NCSE were dichotomized into a “fast” criterion group (> 25 EDs/10 s) and a “slow” criterion group (EDs or rhythmic delta activity (RDA) at a frequency of < 25/10 s). In order to fulfill the slow criterion, one of three additional sub-criteria had to be attained. These included (i) morphological, temporal or spatial evolution of epileptic activity, (ii) electroencephalographic as well as clinical response to an intravenous anti-seizure medication (ASM) trial, or (iii) demonstration of subtle clinical ictal phenomena at the time of EEG acquisition. Possible NCSE according to the SC [4] was diagnosed in case of slow epileptic discharges or RDA, which did not meet any of the three subcriteria, but had (i) electroencephalographic improvement without clinical improvement after intravenous ASM or (ii) fluctuation without evolution.

The SC had not been applied at the time of primary EEG evaluation, and analysis required retrospective evaluation of EEGs. Data collected for analyses included the SC and other EEG features as part of the EMSE. EEG evaluators (OSM, LER, TK) were blinded to clinical outcome to minimize observer bias. EEGs were initially evaluated by OSM and LER. In case of disagreement or controversy the EEG was evaluated by TK to make the final diagnosis. EEGs had been recorded on a NicoletOne Neurodiagnostic system (Natus Neurology, Middleton, USA) according to the international 10–20 system using an average reference (all active electrodes) and a ground electrode on the forehead. They were standard 30 min recordings.

Covariates

Demographic data included age, sex, somatic and psychiatric comorbidity and nationality. The severity of NCSE was estimated based on treatment data, the duration of the SE episode and duration of hospital admission. NCSE was classified based on the degree of impaired awareness, whether it was preceded or succeeded by convulsive SE and its causative etiology according to the International League Against Epilepsy (ILAE) [15]. Refractory NCSE was defined as persistent seizures despite appropriate use of two intravenous medications. Superrefractory NCSE was defined as status epilepticus that continued or recurred 24 h or more after the onset of anesthetic therapy. To address potential confounding factors, components of validated prognostic scoring systems in SE (STESS, EMSE) [7–9] were included in the multivariate analysis. All the individual components of the STESS and EMSE scores were collected. Only the individual components of the STESS score, and comorbidity from the EMSE score, were included in the statistical analysis, as too many independent variables would interfere with statistical assumptions of our regression analysis. We excluded the following components of the EMSE score from statistical analysis: 1. The age component of the EMSE score was redundant as it was included in STESS. 2. Etiology according to EMSE included too many variables. 3. The EEG component was redundant, as were already assessing EEG criteria.

The Charlson comorbidity index [16] was determined as a subscale of the EMSE.

Outcomes

The primary outcome of this study was long-term survival, which was based on data from the Danish Central Person Registry at the time of electronic medical record extraction. Survival status was available for all patients. Minimum follow up was two years.

Secondary outcomes included changes in neurological function from baseline (estimated status before admission) measured using the National Institute of Health Stroke Scale (NIHSS) and changes in the degree of functional independence in activities of daily living, measured with the Barthel Index and modified Rankin Scale (mRS) following the SE episode. NIHSS and mRS scores were approximated from neurological exams and clinical information, as they had not been documented directly in every patient.

Statistical analyses

Statistical analyses were performed using IBM SPSS version 26.0 statistical software (results presented) and the statistical software package ‘R’ (www.r-project.org) version 3.6.0 (‘Planting of a Tree’).

Prior to main analyses, demographics and the severity of SE in patients fulfilling fast and slow criteria were compared to identify potential confounders.

The association of the fast criterion with long-term outcome was quantified in a univariate logistic regression analysis with survival status at 2 years following SE as the dependent variable. Results were adjusted for established prognostic factors (etiologic according to ILAE, components of the STESS and EMSE) [2,17] in a multivariate logistic regression model. All variables were incorporated in the model by forced entry. The model coefficients for the “electroclinical syndromes” etiology group according to ILAE yielded large standard errors due to the small number
of participants (n = 3) and was therefore excluded. Statistical significance was assessed through the $\chi^2$ (chi square) statistic, and the overall fit of the model with Cox and Snell $R^2$. Effect sizes of individual model coefficients were determined with the Wald statistic, and parameter estimates were accompanied by bias-corrected and accelerated bootstrapped 95% CIs. The significance level was set at $p < 0.05$. No correction for multiple statistical comparisons were made as there was only one pre-defined primary outcome. For exploratory analyses, the significance level was set at $p < 0.01$ to reduce the risk of type 1 error. To account for overdispersion, results were reproduced using the statistical software R, which yielded similar results. No statistical assumptions related to logistic regression analysis were violated [18].

Statistical significance was determined using the $t$ statistic, and effect size was measured using Cohen $d$. The PROCESS tool (version 3.5; Andrew F. Hayes) was used to perform follow-up mediation analysis.

Exploratory analyses were carried out to investigate (i) the association between the fast and slow criteria and short-term survival, (ii) the association between fulfillment of different subcomponents of the slow criteria and long-term survival, and (iii) the clinical characteristics and prognosis in patients classified as possible NCSE.

Finally, we performed a sample size calculation based on the effect size determined in the logistic regression analyses of 2 year survival, the relative frequencies of the fast and slow criteria, a significance level of 0.05 and a power of 0.8 to be used in future studies. We used StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC for this analysis.

**Ethics and permissions**

The study was approved by the National Health Authorities (3–3013–26611). Access to medical records was approved by the Danish Patient Safety Authority, and permission for data handling was given by the regional Danish Data Protection Agency (18–58576). Due to its observational nature, approval by the Ethics Committee was not required for the study.

**Results**

**Population**

A total of 2189 patients were identified from 2014 to 2017 (Fig. 1). Of these, 2056 patients were excluded according to exclusion criteria; duplicates were removed. Of the remaining 133 patients with suspected
Table 1
Baseline characteristics of 106 adult patients and classification of their first non-convulsive status epilepticus episode.

| Age | Total cohort (n = 106) | Fast diagnostic criterion (n = 57) | Slow diagnostic criterion (n = 49) | Possible NCSE (n = 27) | Group differences (Fast and slow) |
|-----|------------------------|----------------------------------|----------------------------------|------------------------|----------------------------------|
|     |                       |                                  |                                  |                        | Effect size^2 (95% CI) p         |
| < 50 yr. | 8 (7.5) | 7 (12.3) | 1 (2.0) | 3 (11.1) |                       |
| 50–59 yr. | 16 (15.1) | 10 (17.5) | 6 (12.2) | 5 (18.5) |                       |
| 60–69 yr. | 24 (22.6) | 12 (21.1) | 12 (24.5) | 7 (25.9) |                       |
| 70–79 yr. | 27 (25.5) | 11 (19.3) | 16 (32.7) | 6 (22.2) |                       |
| 80–89 yr. | 25 (23.6) | 13 (22.8) | 12 (24.5) | 6 (22.2) |                       |
| > 90 yr. | 6 (5.7) | 4 (7.0) | 2 (4.1) | 0 (0.0) |                       |
| Gender | Male | 52 (49.1) | 27 (47.4) | 25 (51.0) | 16 (59.3) | OR 0.86 (0.40 - 1.86) 0.708 |
|       | Female | 54 (50.9) | 29 (52.6) | 22 (49.0) | 10 (38.7) |                       |
| Nationality | Danish | 101 (95.3) | 54 (95.0) | 47 (96.0) | 24 (88.9) | OR 0.77 (0.12 - 4.78) 0.775 |
|       | Non-Danish | 5 (4.7) | 3 (5.6) | 0 (0.0) | 0 (0.0) |                       |
| Cohort | 2014 | 18 (17.0) | 9 (15.8) | 9 (18.4) | 5 (18.5) |                       |
|       | 2015–2017 | 88 (83.0) | 48 (84.2) | 40 (81.6) | 22 (81.5) |                       |
| Comorbidity | Charlson comorbidity index | 4.0 ± 3.0 | 4.9 ± 3.7 | 3.9 ± 2.7 | 3.8 ± 2.5 | d = 0.30 (0.08 - 0.69) 0.121 |
|       | EMSE comorbidity | 0 (0 - 40) | 0 (0 - 60) | 0 (0 - 40) | 0 (0 - 60) |                       |
|       | Previous epilepsy | 32 (30.2) | 15 (26.3) | 17 (34.7) | 15 (55.6) | OR 0.67 (0.29 - 1.54) 0.350 |
| Baseline daily function | Neurological | 0 (0 - 4) | 0 (0 - 3) | 0 (0 - 4) | 1 (0 - 8) | d = 0.10 (0.28 - 0.48) 0.610 |
|       | NIHSS | 1.6 ± 1.3 | 1.8 ± 1.4 | 1.8 ± 1.4 | 1.9 ± 1.7 | d = 0.04 (0.34 - 0.42) 0.845 |
|       | Barthel index | 100 (80 - 100) | 100 (83 - 100) | 100 (78 - 100) | 100 (65 - 100) | d = 0.00 (0.02 - 0.02) 0.998 |
| Etiology according to ILAE | Acute symptomatic | 51 (48.1) | 31 (54.4) | 20 (40.8) | 8 (29.6) | OR 1.73 (0.80 - 3.74) 0.165 |
|       | Remote symptomatic | 23 (21.7) | 10 (17.5) | 13 (26.5) | 8 (29.6) | OR 0.59 (0.23 - 1.50) 0.266 |
|       | Progressive CNS disorder | 19 (17.9) | 10 (17.5) | 9 (18.4) | 5 (18.5) | OR 0.95 (0.35 - 2.56) 0.912 |
|       | Status epilepticus in defined electroclinical syndrome | 2 (1.9) | 2 (3.5) | 0 (0) | 1 (3.7) |                       |
|       | Cryptogenic (unknown) | 11 (10.4) | 4 (7.0) | 7 (14.3) | 5 (18.5) | OR 0.45 (0.12 - 1.65) 0.230 |
| Classification of status epilepticus^2 | Focal NCSE without impairment of awareness | 18 (17.0) | 10 (17.5) | 8 (16.3) | 6 (22.2) | OR 1.09 (0.39 - 3.02) 0.868 |
|       | Focal or generalized NCSE with mild to moderate impairment of awareness^2 | 46 (43.4) | 26 (45.6) | 20 (40.8) | 11 (40.7) | OR 1.22 (0.56 - 2.63) 0.619 |
|       | NCSE in coma | 51 (48.1) | 28 (49.1) | 23 (46.9) | 12 (44.4) | OR 1.09 (0.50 - 2.34) 0.823 |
|       | Convulsive status epilepticus preceding or succeeding NCSE | 20 (18.9) | 14 (24.6) | 6 (12.2) | 7 (25.9) | OR 2.33 (0.82 - 6.64) 0.112 |
|       | Proportion convulsive with generalized convulsive status epilepticus | 9 (45.0) | 5 (36.0) | 4 (67.0) | 7 (100) |                       |
| Severity and treatment of status epilepticus | Days in status epilepticus | 4.5 (2.2 - 7.9) | 4.1 (2.0 - 7.4) | 6.0 (2.9 - 8.8) | 1.0 (0 - 4.0) | d = 0.05 (0.33 - 0.44) 0.781 |
|       | Total days of hospitalization | 16 (9 - 16) | 15 (8 - 38) | 24 (10 - 40) | 9 (20) | d = 0.09 (0.29 - 0.47) 0.641 |
|       | Number of anti-seizure medications | 2.8 ± 1.1 | 2.9 ± 1.1 | 3.0 ± 1.0 | 2.3 ± 1.0 | d = 0.06 (0.32 - 0.45) 0.746 |
|       | Refractory NCSE | 84 (79.2) | 45 (78.9) | 39 (79.6) | 14 (51.9) | OR 0.96 (0.37 - 2.47) 0.935 |
|       | Treated at the intensive care unit | 38 (35.4) | 21 (36.8) | 17 (34.7) | 10 (37.0) | OR 1.10 (0.49 - 2.44) 0.818 |
|       | Super refractory NCSE | 17 (16.0) | 7 (12.3) | 10 (20.4) | 1 (3.7) | OR 0.55 (0.19 - 1.56) 0.260 |
| Prognostic scores in status epilepticus | EMSE total score | 76.3 ± 32.8 | 86.3 ± 35.1 | 74.5 ± 29.5 | 55.8 ± 24.7 | d = 0.36 (0.02 - 0.75) 0.565 |
|       | STESS total score | 4.0 ± 1.8 | 3.9 ± 1.9 | 4.1 ± 1.8 | 2.9 ± 1.6 | d = 0.11 (0.27 - 0.49) 0.067 |

Numerical data are presented according to distribution: Normal data with mean ± SD, non-normal data with median (lower interquartile range - higher interquartile range), and counts with number (percentage). P-values without correction for multiple comparisons.

EIEG, electroencephalogram; SD, standard deviation; ILAE, International League Against Epilepsy; NCSE, non-convulsive status epilepticus; CNS, central nervous system; EMSE, epidemiology-based mortality scores in status epilepticus; STESS, Status Epilepticus Severity Score.

^2 Effect sizes are displayed as Odds Ratios for categorical data and Cohen’s d for numerical data. The slow criterion of the Salzburg Criteria is used as reference (denominator).

^1 All other patients classified as non-Danish including Nordic, European, Non-European subdivisions.

^2 Known epilepsy or treatment with antiseizure medications.

^3 Patients can be grouped into several categories.

^4 Focal SE with impaired awareness, typical absence SE and atypical absence SE.

NCSE on EEG, 27 did not fulfill the SC. Hence, a total of 106 patients were included with definite first-time NCSE according to the SC, and these were enrolled in the main analysis. Of the 27 who did not fulfill the main SC, 13 met the SC for possible NCSE. The remaining 14 patients had clinical signs of NCSE, but the available EEGs for these patients were without ictal activity, presumably due to fluctuations in ictal activity. These 27 patients were classified as possible NCSE and included in exploratory analyses. Mean follow-up time to death or drop-out for the entire cohort was 17.7 months.
Baseline characteristics and details regarding the SE episodes for patients fulfilling the fast and slow criteria are presented in Table 1. Of the baseline characteristics, only comorbidity according to EMSE differed between the groups with a moderate effect size ($p = 0.020, \delta = 0.46, 95\% CI 0.07–0.85$). None of the variables included in Table 1 had missing data.

Mortality rates at different time points of follow-up are shown in Table 2, and survival curves for the slow SC subcriteria are presented in Fig. 2. In the total cohort, 69/106 (65.1\%) patients died during follow-up. Probability of survival decreased most during the first year after the SE episode and stabilized after approximately 2 to 3 years (Fig. 2A). Survival curves for the diagnostic criteria were initially inseparable for about 40 to 50 days after initiation of the SE episode, after which they separated with a log-rank test ($p < 0.001$).

Overall, neurological deficits (NIHSS) increased by a mean of 7.07 (95\% CI 5.29–8.91) from baseline to discharge. Functional independence in activities of daily living decreased, reflected in a mean reduction in Barthel Index of 42.8 (95\% CI 34.76–51.22) and a mean increase in mRS of 1.80 (95\% CI 1.49–2.15). The functional outcome did not differ between patients in fast and slow criteria groups.

SC and survival after 2 years

Logistic regression analyses of the fast criterion and other variables for 2-year survival are presented in Table 3. After correction for adjusting variables, the fast criterion was significantly associated with 2-year survival status (OR 0.31, 95\% CI 0.11–0.85, $p = 0.039$). The Charlson comorbidity score was also associated with 2-year survival status (excluding age points, OR 1.04, 95\% CI 1.01–1.06, $p = 0.003$). A follow-up mediation analysis confirmed that the patients level of comorbidity influenced the effect of the fast criterion on 2-year survival ($\beta = 0.46$).

Exploratory analyses

Slow diagnostic criterion subcriteria and long-term survival.

Survival curves for each subcategory of the slow criterion are presented (Fig. 2B-D). EEG findings from patients classified as possible NCSE ($n = 27$) were added to this analysis. Log-rank tests revealed no significant differences in survival.

Salzburg criteria and short-term survival

In a multivariate logistic regression model, the fast criterion was not significantly associated with 3-month survival status following NCSE before (OR 0.566, 95\% CI 0.256–1.252, $p = 0.44$) or after (OR 0.366, 95\% CI 0.122–1.097, $p = 0.073$) adjustment for potential confounders as described in the main analysis. Comorbidity (OR 1.031, 95\% CI 1.008–1.055, $p = 0.007$) was significantly associated with short term survival.

Characteristics of patients classified as possible NCSE

Follow-up analyses of the 27 patients classified as possible NCSE (Table 1) revealed several significant differences from patients fulfilling the SC. These patients more often suffered from non-refractory SE (OR 3.55, 95\% CI 1.46–8.62, $p = 0.005$) and had fewer anti-seizure medications ($t_{31} = 3.039, p = 0.003$, Cohen $d = 0.66$, 95\% CI 0.22–1.08). STESS ($t_{131} = 2.928, p = 0.004$, Cohen $d = 0.63$, 95\% CI 0.20–1.06) and EMSE ($t_{131} = 3.690, p < 0.001$, Cohen $d = 0.80$, 95\% CI 0.36–1.23) scores were significantly lower, and NIHSS ($t_{63} = 3.302, p = 0.002$, Cohen $d = 0.71$, 95\% CI 0.27–1.15) and Barthel Index scores ($t_{52} = 3.438, p = 0.001$, Cohen $d = 0.74$, 95\% CI 0.29–1.18) changed significantly less. Survival curves for patients fulfilling the SC compared to those classified as possible NCSE are presented in Fig. 2A.

Sample size calculation

Based on the findings of the logistic regression analyses of 2 year survival with an effect size of OR 0.31 and an assumption of a 1:1 ratio between the fast and slow criterion we estimated a total sample size of $n = 104$.

Table 2

Mortality and morbidity in 106 adult patients following first-time NCSE according to the Salzburg Criteria.

| Group differences | 95\% CI for effect size $p$ |
|-------------------|---------------------------|
| Mortality according to time of follow-up - no. (%) | 
| Discharge 24 (22.6) | 12 (21.1) | 12 (24.5) | OR 0.82 | 0.33 | 2.04 | 0.67 |
| 3 months 40 (37.7) | 18 (31.6) | 22 (44.9) | OR 0.57 | 0.26 | 1.25 | 0.16 |
| 2 years 61 (57.5) | 29 (50.9) | 32 (65.3) | OR 0.55 | 0.25 | 1.21 | 0.14 |
| At data closure 65 (61.3) | 31 (54.4) | 34 (69.4) | OR 0.53 | 0.24 | 1.17 | 0.12 |

Neurological

Increase in NIHSS $7.1$ [5.2–8.9] $6.3$ [3.9–8.6] $8.1$ [5.0–11.1] $d = 0.19$ $0.20$ 0.57 $0.35$

Degree of functional independence in activities of daily living

Increase in mRS $1.8$ [1.5–2.2] $1.7$ [1.3–2.3] $1.9$ [1.4–2.4] $d = 0.06$ $0.32$ 0.44 $0.76$

Decrease in Barthel Index $43$ [35–51] $43$ [32–55] $42$ [30–55] $d = 0.02$ $0.37$ 0.40 $0.94$

NCSE, non-convulsive status epilepticus; CI, confidence interval; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale.

$^a$ Confidence intervals were estimated with the Bias-corrected and accelerated bootstrap method (1000 bootstraps).

$^b$ Effect sizes are displayed as Odds Ratios for categorical data and Cohen $d$ for numerical data. The slow criterion of the Salzburg Criteria is used as reference (denominator).
Discussion

In this retrospective cohort study, approximately two-thirds of the adult patients with first-time NCSE from 2014 to 2017 were dead after 2 years of follow-up. The fast criterion was significantly associated with favorable survival status after NCSE and may represent a new prognostic marker for long-term mortality. Short-term mortality rates in patients with NCSE were previously reported to be 18, [19] 37, [20] 52, [21] 57 [22] and 79% [23] depending on inclusion of anoxic etiology, patient age and the clinical setting. Our in-hospital mortality rate of 22.6% is comparable to short-term case-fatality rates seen in patients with convulsive SE [1] and the short-term mortality described by Shneker and Fountain [19], one of the largest retrospective cohort studies in patients with non-anoxic NCSE to date. Further, this study confirms the substantial increase from in-hospital to long-term mortality at 2 years of follow-up as previously reported [6] and suggests that the results are generalizable to patients with NCSE.

There is great controversy as to whether NCSE causes permanent brain damage [3,28–34] whereas NCSE in coma is associated with substantial morbidity [38]. The considerable neurological deficits and decreased independence in activities of daily living at discharge described in our study may partly be attributable to the large proportion of patients with NCSE in coma, representing about half of the study sample. However, this is unlikely to be the only cause, and other factors, such as the length of NCSE, time of diagnosis, etiology and fulfillment of the slow criterion must be accounted for in future studies with increased statistical power to further investigate the causes of brain damage in patients with NCSE.

Prediction of long-term survival in patients with NCSE is difficult with the current prognostic scoring systems [10–12] and needs supplementation. Non-EEG predictors of short-term mortality in NCSE include the underlying etiology of NCSE, its subtype and refractoriness to treatment, acute medical complications during admission, number of comorbidities including history of epilepsy and treatment with benzodiazepines in the elderly population [16,19,22,23,38,39]. In our exploratory analyses, comorbidity was significantly associated with survival status at 3 months.

Theoretical ground for our working hypothesis was provided by a study by Witsch et al., [40] which demonstrated a statistically significant inverse relationship between the local tension of oxygen in brain tissue and the frequency of periodic epileptiform discharges, implying greater potential for subsequent brain damage with high frequency
Table 3

Adjusted and unadjusted association of the Salzburg Criteria with mortality in 106 adult patients two years after first-time non-convulsive status epilepticus.

| Model coefficients | 95% CI for Odds Ratio for 2 year death<sup>1</sup> |
|---------------------|-----------------------------------------------|
| Unadjusted<sup>2</sup> |                                                |
| Constant            | 0.63 (0.30) 1.88 0.029                        |
| Adjusted<sup>3</sup> | Fast versus slow criterion                    |
| Constant            | −0.60 (0.40) 0.55 0.25 1.21 0.150              |
| Adjusted<sup>3</sup> | Fast versus slow criterion                    |
| Constant            | 0.78 (0.94) 1.08 0.946                        |
| STESS components    | Age (> 65 vs < 65 years)                      |
|                     | 0.61 (0.53) 1.84 0.65 5.18 0.248              |
| History of epilepsy | −0.06 (0.53) 0.95 0.33 2.68 0.916              |
| Worst seizure type  | Focal, absence, myoclonic                     |
| vs non-convulsive status epileptic in coma | −0.87 (0.83) 0.42 0.08 2.13 0.296 |
| Generalized convulsive vs non-convulsive status epileptic in coma | −0.24 (0.68) 0.79 0.21 2.95 0.721 |
| Level of consciousness | Stuporous to comatose vs alert to somnolent/confused | 0.04 (0.71) 1.04 0.26 4.17 0.953 |
| Etiology according to ILAE | Remote symptomatic vs acute symptomatic | −1.13 (0.61) 0.32 0.10 1.06 0.063 |
|                        | Progressive CNS disorder vs acute symptomatic | 0.62 (0.73) 1.86 0.45 7.79 0.395 |
|                        | Cryptogenic vs acute symptomatic               | 0.63 (0.79) 1.89 0.40 8.82 0.422 |
| Comorbidity (EMSE)    | 0.04 (0.01) 1.04 1.01 1.06 0.003               |

CI, confidence intervals; STESS, Status Epilepticus Severity Score; ILAE, International League Against Epilepsy; CNS, central nervous system; EMSE, Epidemiology-based Mortality score in Status Epilepticus.

<sup>1</sup> Bias-corrected and accelerated bootstrapped Confidence Interval (based on 1000 bootstrap samples).

<sup>2</sup> Unadjusted univariate logistic regression model: R<sup>2</sup> = 0.02 (Cox-Snell).

<sup>3</sup> Adjusted multivariate logistic regression model: R<sup>2</sup> = 0.22 (Cox-Snell).

epileptic activity.

Few studies have investigated the short-term prognostic value of EEG features in SE [1,19,41-44] Notably, Shneker and Fountain [19] evaluated the association of the frequency of epileptic activity and short-term survival in an exploratory analysis, but neither this nor other EEG features were significant predictors.

Opposite to our working hypothesis, our findings indicate a significant association between high frequency of epileptic discharges and long-term survival in patients with first-time NCSE. This association was evident after about 40 to 50 days, presumably linked to the fact that the risk of death due to the underlying etiology of SE and acute complications during hospitalization overshadow the obvious slow criterion. It is quite possible that subcriteria constituting the slow criterion are responsible for most of the association with long term survival, and that increased statistical power or adjustment for established prognostic factors in a Cox proportional hazards model could clarify their individual importance in future studies.

Our interpretation is that a “low frequency EDs” seen in patients with EEG-verified NCSE represent a “damaged decompensating brain”, in which EDs may reflect structural brain damage rather than epileptic brain dysfunction. As aggressive treatment with intravenous anti-seizure medications and sedatives is associated with considerable side effects, these treatment options should be tailored to patients where the risks of aggressive treatment does not exceed the benefits of more conservative strategies [3]. Stratification of patients with NCSE according to the SC may be useful in guiding clinical management.

Our sample size estimation suggests that future prospective studies will be feasible.

Study limitations

Most patients only had one or a series of standard 30 min EEG acquisitions. If fulfillment of the SC subcriteria fluctuates in the same patient, it is possible that analysis of standard EEG acquisitions has biased our results. Continuous EEG studies have shown that approximately 50% of patients with an initial presentation of periodic discharges will later have electrographic seizures [45,46]. Continuous EEG monitoring would enable quantification of time spent in different frequency strata of ictal activity. This information, combined with clinical outcomes and surrogates of neuronal brain damage, such as neuron-specific enolase [35-37] or neuroimaging [47,48] could further determine the degree to which the frequency of ictal epileptiform discharges influences morbidity and mortality in patients with NCSE.

Another limitation is the retrospective estimation of the NIHSS. Estimation was based on information available from medical records, and does not reflect an exact evaluation of the neurological status.

Study strengths

Linkage of the Danish Civil Registration System and the patient electronic medical records enabled complete long-term follow up, with minimal missing data (<2%). Evaluation of medical records and EEG examination was done separately and blinded to minimize the risk of observer bias. Missing cases of subtle NCSE resulting in ascertainment bias when assessing outcome, was avoided by early diagnosis of SE whenever it exceeded its temporal threshold for treatment initiation [18].

Because patients with a minimal suspicion of NCSE are referred for EEG evaluation, and identification of patients with NCSE was supplemented with ICD-10 codes, the study approximates NCSE in the population. The sample size from our study surpasses many previously conducted studies on adult patients with NCSE, [19,22-24,30,38,39] and carries similar in-hospital and long-term mortality rates [6,19]. It employs transparent and validated classifications of SE, [15] and results were adjusted for established prognostic determinants for patients with SE [2,7,16].

Conclusions

The fast diagnostic electroencephalographic criterion for NCSE was significantly associated with favorable survival status at 2 years of follow-up after controlling for established prognostic factors. Further, patients classified as possible NCSE had a better prognosis compared to patients fulfilling the Salzburg criteria, possibly acting as a surrogate marker for several clinical differences. Our results could allow prognostication in patients with NCSE already at the time of diagnosis, and should be investigated as part of prognostic scores in future studies in order to improve prediction of survival and guide clinical management of these patients.

Conflicts of interest

Christoph P. Beier has received funding from UCB and Eisai. The other authors report no conflicts of interest.

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