Surviving the Storm—Surviving Status Epilepticus

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Prediction of Long-term Survival After Status Epilepticus Using the ACD Score
Roberg LE, Monsson O, Kristensen SB, Dahl SM, Ulvin LB, Heuser K, Taubell E, Strzelczyk A, Knake S, Bechert L, Rosenow F, Beier D, Beniczky S, Krøigaard T, Beier CP. JAMA Neurol. 2022;79(6):604-613. doi:10.1001/jamaneurol.2022.0609

Importance: Early prediction of long-term mortality in status epilepticus is important given the high fatality rate in the years after diagnosis. Objective: To improve prognostication of long-term mortality after status epilepticus diagnosis. Design, Settings, and Participants: This retrospective, multicenter, multinational cohort study analyzed adult patients who were diagnosed with and treated for status epilepticus at university hospitals in Odense, Denmark, between January 1, 2008, and December 31, 2017, as well as in Oslo, Norway; Marburg, Germany; and Frankfurt, Germany. They were aged 18 years or older and had first-time, nonanoxic status epilepticus. A new scoring system, called the ACD score, for predicting 2-year (long-term) mortality after hospital discharge for status epilepticus was developed in the Danish cohort and validated in the German and Norwegian cohorts. The ACD score represents age at onset, level of consciousness at admission, and duration of status epilepticus. Data analysis was performed between September 1, 2019, and March 31, 2020. Exposures: Long-term follow-up using data from national and local civil registries in Denmark, Norway, and Germany. Main Outcomes and Measures: The predefined end point was 2-year survival for all patients and for a subgroup of patients with status epilepticus causes that were not damaging or were less damaging to the brain. Neurological deficits before and after onset, demographic characteristics, etiological categories of status epilepticus, comorbidities, survival, time points, treatments, and prognostic scores for different measures were assessed. Results: A total of 261 patients (mean [SD] age, 67.2 [14.8] years; 132 women [50.6%]) were included, of whom 145 patients (mean [SD] age, 66.3 [15.0] years; 78 women [53.8%]) had status epilepticus causes that were not damaging or were less damaging to the brain. The validation cohort comprised patients from Norway (n = 139) and Germany (n = 906). At hospital discharge, 29.8% of patients (n = 64 of 215) had new moderate to severe neurological deficits compared with baseline. New neurological deficits were a major predictor of 2-year survival after hospital discharge (odds ratio, 5.1; 95% CI, 2.2-11.8); this association was independent of etiological category. Nonconvulsive status epilepticus in coma and duration of status epilepticus were associated with development of new neurological deficits, and a simple 3-factor score (ACD score) combining these 2 risk factors with age at onset was developed to estimate survival after status epilepticus diagnosis. The ACD score had a linear correlation with 2-year survival (Pearson r² = 0.848), especially in the subset of patients with a low likelihood of brain damage. Conclusions and Relevance: This study found that age, long duration, and nonconvulsive type of status epilepticus in coma were associated with the development of new neurological deficits, which were predictors of long-term mortality. Accounting for risk factors for new neurological deficits using the ACD score is a reliable method of prediction of long-term outcome in patients with status epilepticus causes that were not damaging or were less damaging to the brain.

Commentary
Throughout history, mariners tried to forecast the most feared consequence of sailing, the storm, to improve their survival, until Irishman Francis Beaufort developed the Beaufort wind scale in 1805. Status epilepticus (SE) is our storm in the field of epilepsy—where 1 year mortality is over 20%, with many more cases...
patients not surviving unscathed, a phenomenon still poorly understood.\(^1\) We need more data on outcomes in SE, to plot a better course for our patients and their families.

Roberg et al\(^2\) studied over 1000 adult cases of status epilepticus, and developed and validated the age, consciousness, duration (ACD) score, to predict neurological deficits, and in turn, 2-year survival from SE. They performed a retrospective cohort study in Denmark between 2008 and 2017 of risk factors associated with long-term outcome of both convulsive SE and non-convulsive SE (NCSE). The ACD score was validated in 2 independent cohorts of patients in Norway and Germany.

Mortality of the whole cohort during hospitalization was 17.6%. Long-term mortality at 2 years was 47.1%. Nine patients with absence SE had no neurological deficits and were alive at 2 years, in line with the better prognosis in this form of SE.

In a complex staged design, they first performed a logistic regression model of variables for 2-year survival after SE, finding that older age, neurological deficits, and progressive central nervous system (CNS) disease were negatively associated with survival.

Given the strong link with neurological deficits, they performed a linear regression model looking for predictors of new neurological deficits. Neurological deficits were measured by change in the National Institutes of Health Stroke Scale (NIHSS) from before SE to first follow-up or hospital discharge. The NIHSS is not validated in SE, would overestimate scores in the setting of impaired awareness, and does not measure cognitive deficits. The scores were also retrospectively estimated from examination records. However, no alternative score is available for SE outcome research, so one is sorely needed. Median survival was only 34.2 months for NIHSS 5–10 and 3.4 months for NIHSS >10. The duration of SE was the common factor among both the whole cohort and in a subgroup of “less-damaging” causes. The authors conclude that duration of SE, NCSE in coma, and age were associated with new neurological deficits and in turn, predictors of 2-year survival.

They developed the ACD score in the less-damaging cohort, by using a logistic regression model with Least Absolute Shrinkage and Selection Operator (LASSO) for short-term survival at 2 years without a neurological deficit and found 5 predictors—age, log of duration, level of consciousness on admission, intensive care unit treatment, and time to diagnosis. They removed the last 2 weaker associations to form the ACD score. In this analysis, NCSE or other factors such as refractory SE or comorbid conditions were not associated with survival.

LASSO is a statistical technique using shrinkage, a form of linear regression where data values are shrunk toward the mean, encouraging models with fewer parameters, with more accurate prediction.

Age at diagnosis of SE, level of consciousness on admission, and duration of SE were included in the ACD score, with points allocated for age in years (<40 years, >40 years, >60 years, >80 years), duration of SE (graded from <1 to 400 hours), and level of consciousness on admission (awake/somnolent or stuporous/coma). The score had a linear relationship with mortality at 2 years. Optimal cutoff value of the ACD score was <10 for being alive without new deficits at first follow-up, with a sensitivity of 0.63 and specificity of 0.82. The authors provide a nomogram, plotting points for the 3 factors into total points and projected percent 2-year mortality.

The study provides insight into the contribution of seizure-induced neuronal injury to outcome in SE. Direct injury from etiology is certainly the case for those with anoxic or hypoglycemic brain damage who were excluded from the study, and for patients included with progressive CNS disorders. The answer is less clear for other causes. The authors analyzed a subset of patients with “nondamaging or less-damaging” causes of SE, similar in demographics to the whole cohort. These included nonadherence, alcohol, mild dementia, drug induced, and SE due to remote symptomatic or unknown causes as opposed to acute symptomatic causes such as stroke, hemorrhage, infection, and progressive CNS disease. While the authors defined SE due to remote symptomatic epilepsy, generalized epilepsy, and unknown causes as “less damaging,” in clinical practice these could cause as much neuronal injury as status from a “damaging” cause such as a brain tumor. Increased mortality is seen after other brain injuries, and even mild traumatic brain injury was associated with an increased 5-year mortality risk.\(^3\)

NCSE causes neuronal damage in animal models,\(^4\) supporting the clinically observed outcome in this study for increased risk of neuronal damage in SE measured by the development of neurological deficits and increased long-term mortality in patients with NCSE.

The study has flaws, including incongruous use of survival for mortality, and NCSE in coma with level of consciousness on arrival, but the overall conclusions are valid. The study was retrospective, and what we really need are prospective studies that will also judge the effect of interventions such as earlier use of benzodiazepines, earlier recognition and treatment of NCSE, and clinical trials of treatment for refractory SE. The study was strengthened by almost complete follow-up of a large number of patients using national registries.

Do we need another acronym score for SE? The Status Epilepticus Severity Score (STESS) predicts in hospital mortality but not long-term outcome.\(^5\) The epidemiological mortality in status epilepticus score (EMSE)\(^6\) predicts long-term survival but has complex scoring and is etiology based—etiology has long been a controversial confounding factor in SE outcomes, but apart from progressive CNS disease, etiology did not seem to predict long-term outcome in this study. What all these patients have in common is prolonged electrochemical activation of brain neuronal networks.

In practice, the ACD nomogram should help us counsel our patients and caregivers and identify patients at most risk for both clinical and research purposes.

In the Established status epilepticus treatment trial (ESETT), over 50% of SE patients were still seizing after second line therapy.\(^7\) We need to combine bench and clinical research to better understand the pathophysiological
mechanisms behind neurological deficits due to SE. How does post-SE epilepsy or the presence of diffusion-weighted or hypoxic changes on magnetic resonance imaging contribute to mortality risk? However, as Roberg’s study also shows, not everyone with SE has a bad outcome. SE is an avoidable cause of mortality in epilepsy.

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