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Clinical scores and clusters for prediction of outcomes in status epilepticus

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ABSTRACT

Status epilepticus (SE) is a life-threatening condition and may have long-term negative sequelae. Short- and long-term outcomes encompass mortality, deterioration of functional status compared to baseline, refractoriness to treatment, recurrence of SE, and development of epilepsy, cognitive impairment, and behavioral disturbances. So far, the greatest amount of evidence is available for the prediction of short-term mortality. Conversely, the knowledge regarding long-term consequences among SE survivors is still scarce and several issues have not yet been resolved. The heterogeneity of SE renders the prognostication of outcomes challenging. Although aetiology is the main determinant of the outcome, different prognostic predictors have been identified. In this regard, data on group effects need to be integrated into prognostic scores to allow individual risk stratification. Importantly, many of the present scores are not designed to enable repetition to follow patient evolution. A new paradigm for the assessment of SE outcomes should consider variables that become available and/or can be retested during the course of SE. Neuroimaging findings, serum biomarkers, treatment characteristics, complications during SE, peri-ictal and postictal characteristics after SE cessation look as promising determinants of outcome and are suitable for inclusion in future models to enhance the quality and increase the reliability of prediction. This paper was presented at the 8th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures held in September 2022.

1. Introduction

Status epilepticus (SE) is a life-threatening condition and may have long-negative term sequelae. Different short- and long-term outcomes may have relevance from the clinical perspective. These may encompass mortality, deterioration in functional status, refractoriness to treatment, recurrence of SE, development of epilepsy, cognitive deficits and behavioral disturbances, and quality of life (Table 1). So far, the greatest amount of evidence is available for the prediction of mortality. Conversely, the knowledge regarding long-term consequences among SE survivors is still scarce and several issues have not yet been resolved [1]. Here, we provide a summary of the currently available key evidence about phenotypic clusters and clinical outcomes in adult patients with SE and suggest directions for future research in the field.

2. Evidence from the literature

2.1. Short- and long-term mortality

Mortality is the most investigated outcome, and the overall rates of fatality at discharge ranged from around 10% to more than 60% across the studies. The most robust risk factors for death in SE include (i) demographics, aetiology, and clinical characteristics (e.g., age, prior history of seizures, underlying aetiology, level of consciousness at onset, status type, the evolution of semiology); (ii) biochemical markers (e.g., serum albumin levels, procalci-

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Table 1
Outcomes in status epilepticus.

Short- and long-term mortality
Deterioration in functional status
Refractoriness to treatment
Recurrence of status epilepticus
Subsequent epilepsy
Cognitive impairment
Development of behavioral disturbances
Quality of life
Healthcare utilization and cost

tonin); (iii) treatment characteristics (e.g., SE duration before treatment, lack of response to first-line drugs, failure of anesthetic tapering-off, number, and duration of anesthetics; (iv) complications (e.g., infections, respiratory failure and/or mechanical ventilation, renal/cardiac dysfunction, metabolic acidosis); (v) EEG characteristics (e.g., periodic discharges after SE) [2]. Some of these variables have been integrated into scoring systems and tools for outcome prognostication (Table 2).

The Status Epilepticus Severity Score (STESS) was the first score developed to estimate in-hospital mortality after non-hypoxic SE in patients older than 16 years [3]. It is a frequently and broadly used clinical scoring system for SE cohorts, and this preeminence results from its ease of calculation using a few clinical characteristics available at SE onset. The STESS includes four variables: consciousness (alert or somnolent/confused versus stuporous or comatose), worst seizure type (focal with or without impaired consciousness/awareness, absence, and myoclonic complicating idiopathic generalized epilepsy versus generalized convulsive versus non-convulsive in a coma), age (younger than 65 years versus 65 years of age or older), and history of previous seizure. The original cut-off value was set at 3 points (STESS-3): score values $\geq$3 predict a higher risk of death after a SE episode. The STESS showed a high negative predictive value for survival (97–100%), but a low positive predictive value for death, which represents its weakest performance characteristic [3,4]. This implies that the STESS identifies patients who are more likely to survive a SE episode while it often fails to identify patients who are more likely to die. A first external evaluation recommended increasing the cut-off value to four points (STESS-4) to optimize the test yield [5].

Different changes have been further made to the original STESS to improve the specificity and positive predictive values, and new versions of the score have been developed. These include the Modified STESS [6] and the Newly Modified STESS (nSTESS) [7] (Table 2). Recently, a retrospective external validation of the STESS through a machine-learning analysis in a cohort of adult patients with non-hypoxic SE identified the seizure type as the most significant predictor of in-hospital mortality, followed by age and level of consciousness at SE onset. Further, the decision tree identified 7 "leaf" nodes, corresponding to different clusters of patients with a potential risk of death ranging from 2.4% to 51% [8].

The Epidemiology-Based Mortality Score in Status Epilepticus (EMSE) was also built to predict in-hospital mortality: published mortality rates for potentially predictive parameters were transformed into points for the score [9]. The physicians who developed this score wondered whether the categories of the STESS could benefit from a more granular approach based on the inclusion of points for each decade of age instead of using one single threshold of 65 years, several etiologies including cerebral anoxia instead of the history of prior seizures, EEG findings and comorbidities. In the original explorative study, the EMSE correctly classified 89.1% of patients and outperformed both the STESS-3 and STESS-4. The superiority of the EMSE over the STESS has been further shown in certain populations, but not in others [9–12]. Of note, the EMSE requires information that may be not readily available at SE onset. Similarly to the STESS, the EMSE also appears particularly accurate and effective in identifying patients who will survive after SE, whereas its performance in predicting mortality is lower and needs to be further improved [13]. A nomogram based on the EMSE parameters has been also proposed, and it showed better predictive accuracy than the EMSE alone in predicting the risk of 30-day mortality after SE [14].

Neither the STESS nor the EMSE includes complications during SE among the included parameters. In a retrospective analysis of the factors associated with death at discharge or within 30 days after discharge in a cohort of 10,924 patients, eleven independent variables remained in the final scoring system, including age, five comorbidities, and five complications of SE, namely shock, acute renal failure, septicemia, pneumonia, and respiratory failure [15]. The highest summation of all risk scores was 28, and the cut-off of 4 was associated with mortality yielding a sensitivity of 78.2% and a specificity of 75.4% The model was validated on a similar population of 10,808 patients; the external validation in other populations and the comparison with other predictive scoring systems are not available, yet.

A new 3-factor scoring system called the ACD score, for predicting 2-year mortality after hospital discharge for SE was developed in a Danish cohort and validated in German and Norwegian cohorts [16]. The ACD score represents the age at onset, level of consciousness at admission, and duration of SE. These three variables have been associated with the development of new neurological deficits, which were negative predictors of long-term survival. Accounting for risk factors for new neurological deficits, the ACD score allows the prediction of long-term outcomes in patients with SE causes that were 'not damaging' or were 'less damaging to the brain'. Data did not, however, elucidate the pathological mechanisms associated with new neurological deficits or the causes of death. Further,

Table 2
Prognostic scores of in-hospital mortality in status epilepticus.

Predictors of outcome in scoring systems				
Status Epilepticus Severity Score (STESS) [Rossetti et al. 2008]	**Modified STESS (mSTESS) [González-Cuevas et al. 2016]**	**Newly Modified STESS (nSTESS) [Huang et al. 2021]**	**Epidemiology-based Mortality score in Status Epilepticus (EMSE) [Leitinger et al. 2015]**	**Risk score predictive of mortality in status epilepticus [Tiamkao et al. 2018]**
Level of consciousness	Level of consciousness	Level of consciousness	Aetiology	Age
Worst seizure type	Worst seizure type	Worst seizure type	Age	Comorbidities
Age	Age	Age	Comorbidities	Complications of SE
History of previous seizures	History of previous seizures	History of previous seizures	EEG	
	Baseline disability (modified Rankin Scale)	Use of thiobarbiturate		
		Number of antiseizure medicines used within the first week		

establishing the exact duration of SE may be a challenge for the ACD score, and the duration may at least partially reflect the severity of the underlying aetiology and thereby affect the expected outcome.

2.2. Functional outcome

The STESS and EMSE scales have been further evaluated to predict the functional outcome. Their performances are, however, inconsistent and these scores do not estimate with high accuracy the degree of worsening compared to baseline [10,12,17,18].

The END-IT score has been specifically developed to predict the 3-month unfavorable outcome, defined as death or dependency on others for activities associated with daily living (modified Ranking Scale score 3–6) [19]. The score consists of five variables: the presence of encephalitis, non-convulsive status epilepticus, diazepam resistance, imaging findings (bilateral lesions/diffuse cerebral edema versus unilateral lesions versus no responsible lesions), and tracheal intubation. The total score ranges from 0 to 6, and the cut-off point is 3. In the derivation cohort, the END-IT score showed a good performance, with a predictive accuracy of 76.2% and an area under the receiver operating characteristic curve of 0.833. The END-IT was developed in a cohort of very young (median age 25.5 years) Asian patients with convulsive SE, having SE caused by encephalitis in more than one-third of the cases, and many requiring mechanical ventilation. This may hamper the generalizability of the score, which does not ideally apply to hospital-based SE cohorts in Western countries with higher median age and encephalitis underlying SE in a minority of patients. Further, the neuroimaging item of END-IT does not take into account the acuteness of lesions, reducing the value of this prognosticator: remote lesions cause SE to increase the score, but they may not necessarily represent negative outcome predictors.

The combination of clinical and biological markers may reflect better the pathophysiological mechanisms involved in SE excitotoxicity and consequences and improve the accuracy to predict the degree of worsening induced by SE. Through the support vector machine analyses, two clinico-biological models have been proposed for the prediction of poor functional outcomes at discharge and long-term (6–12 months) recovery of SE patients [20]. Clinical indicators of the disease severity (SE duration) and functional state before SE (modified Ranking Scale score at baseline) have been integrated with variables that can be obtained quickly in all laboratories and reflect non-neurologic organ failure (hepatic [gamma GT, apolipoprotein B, lipoprotein(a), phospholipids], renal [urea, creatinine], systemic [sodium, potassium, chloride] dysfunctions), brain injury induced by SE [neuron specific enolase], critical illness severity or complications of treatment [platelet count, hemoglobin, white blood cell count]. These models showed a strong discrimination power and might be repeated during the stay of the same patient in the intensive care unit because they rely on data that can be monitored over time.

Neuroimaging data and fluid biomarkers of neuronal/astroglial damage have also been investigated to get insight into neurological deterioration related to SE [21]. Ictal MRI changes were associated with a longer duration of SE and a higher risk of neurological deterioration at discharge irrespective of aetiology [22]. Interestingly, serum neurofilaments light chain at SE onset were found to correlate with SE duration, refractoriness to treatment, and worsening of clinical conditions [23].

2.3. Refractoriness to treatment

Refractoriness to treatment is likely multifactorial and it is difficult to identify reliable predictors [24]. Across the studies, demographic, clinical, EEG, and biochemical variables have been associated with refractoriness or super-refractoriness of SE. They include but are not limited to age, acute aetiology, altered level of consciousness at SE onset, non-convulsive SE, higher modified Ranking Scale score at baseline, periodic lateralized epileptiform discharges, low levels of serum albumin at SE onset, low levels and reduction of uric acid levels over time, inadequate first- and second-line treatments.

Validated scoring systems for the prediction of refractoriness do not exist, however, and this still represents an unmet need in clinical practice. A prediction model of responsiveness may also guide studies comparing the efficacy of different therapeutic strategies. In the perspective of upcoming trials aimed at the early initiation of a combination of antiseizure medications instead of a time-consuming stepwise approach, the early identification of patients at high risk for refractory SE might be useful for the proper selection of the candidates who may most benefit from the combinatorial strategy.

Distinct phenotypes have been recognized within the heterogeneity of SE with prominent motor phenomena and non-convulsive SE, and differences in the responsiveness to treatment contributed to distinguishing the clusters alongside aetiology, semeiology, level of consciousness, and EEG activity [25,26]. Phenotyping the heterogeneity of SE into distinctive electroclinical clusters can contribute to identifying and understanding correlations between pathologic and clinical domains, assessing the intrinsic severity of SE episodes, and the likelihood of response to pharmacological interventions. Clustering SE can pave the way for thinking of SE within the framework of a more comprehensive systematization and represent a prolegomenon for a topologic, multidimensionally integrated classification system, which subsumes and integrates at once multiple domains.

2.4. Recurrence of status epilepticus and epilepsy development

The recurrence of SE after an incident episode involves a significant proportion of patients, ranging from 10.4% to 32% across the different cohorts and lengths of follow-up. So far, however, little attention has been directed toward the recurrence of SE [27–31]. The factors recognized as the most important predictors include the remote and progressive aetiologies and refractoriness/super-refractoriness to treatment.

In a retrospective analysis of a cohort of 430 cases of SE, the overall cumulative proportion of SE recurrences at 30 days, 6 months, 12 months, 24 months, 36 months, and 48 months was 1.6%, 9.5%, 13.0%, 15.8%, 17.1%, and 20.5%, respectively [32]. The highest rate (7.9%) was observed in the first 6 months of the index event. In the analysis by aetiology, the cumulative proportion of SE recurrence at 48 months was 11%, 26%, and 40% in the case of acute, progressive, and remote symptomatic aetiologies. Remote and progressive symptomatic aetiologies and super-refractory SE at the first SE episode were independent predictors of recurrence. With a 6-month cut-off criterion, which was the period with the highest risk of recurrence, patients with the first relapse within six months from the index event had higher STESS values and presented more commonly refractory or super-refractory SE at the time of the incident episode. Further, although there were no differences in the rates of 30-day mortality following the SE relapse between patients with early versus late recurrence, long-term survival was higher in patients with late recurrence SE. The identification of subjects at high risk of recurrent SE would be potentially helpful to adapt and optimize their clinical follow-up.

In animal models, SE induces damage in the brain that results in the reorganization of neural networks. In humans, data about SE-induced brain changes and their clinical implications are scarce. A consistent proportion of patients surviving a SE episode will,

however, develop epilepsy, suggesting that SE can represent, at least in some situations, a major epileptogenic insult [33,34].

The aetiology, duration of SE, and refractoriness to treatment are among the most consistently identified predictors of subsequent epilepsy. In a cohort of 89 patients with SE and without prior history of epilepsy, 58.7% of survivors develop epilepsy after a median follow-up of 10 months [35]. Epilepsy development was directly associated with SE duration and inversely related to toxic-metabolic etiology. Regarding duration, a cut-off of above 24 hours was linked with a higher risk of epilepsy in patients with SE due to acute symptomatic, but not remote/progressive etiology. Focal SE, the presence of a lesion in neuroimaging, and the use of two or more antiseizure medications were suggested to be other potential risk factors for subsequent epilepsy. Looking at specific causes of SE, the risk of epilepsy following post-stroke SE has been investigated [36]. In a cohort of 50 patients with early post-stroke SE followed up for a median of 214 days, the estimated epilepsy rate was 35.3% in the first year and 53.8% in the second year. Both stroke and SE characteristics affected the risk of epilepsy: more severe stroke (National Institutes of Health Stroke Scale score > 4) and longer SE (duration > 16 hours) were independently associated with a greater risk of epilepsy. Interestingly, the latency from SE to epilepsy was shorter in patients with SE longer than 16 hours compared to patients whose SE terminated within 16 hours.

3. Conclusions and future perspectives

The heterogeneity of SE renders the prognostication of outcomes challenging. Although aetiology is the main determinant of outcome [37,38], different prognostic predictors have been identified from a series describing effects on group levels. Biochemical, EEG, and neuroimaging characteristics, which interact with each other in a complex manner, also show promise for outcome prognostication. Data on group effects, however, do not necessarily predict individual outcomes, and they need to be integrated into prognostic scores to allow individual risk assessment and stratification [39]. Of note, scores can assist and support clinical reasoning, but they do not need to be considered as the only criterion to guide decision-making [39].

Importantly, many of the present scores are not designed to enable repetition to follow patient evolution. A new paradigm for the assessment of SE outcomes should consider additional variables that become available and/or can be monitored and retested during the course of SE. Neuroimaging findings, serum biomarkers, treatment characteristics as time from SE onset to treatment and the use of anesthetics, SE duration, complications during SE, periictal and postictal clinical and EEG characteristics after SE cessation look suitable for inclusion in future models to enhance the quality and increase the reliability of prediction [2]. In this regard, the use of "big data" and machine-learning models can allow for the integration of more easily prognostic markers into "personalized medicine" systems [40]. Finally, the implementation of new clinico-biological prognostic scores into electronic devices, once developed and validated, may promote their clinical utilization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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