Original Article

Utility of the END-IT Score to Predict the outcome of Childhood Status Epilepticus: A Retrospective Cohort Study

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Abstract

Introduction: Scoring systems to predict outcomes in pediatric status epilepticus (SE) are limited. We sought to assess usefulness of the END-IT score in pediatric SE. **Methodology:** We conducted a retrospective study at a tertiary hospital in New Delhi, India. Children aged 1 month–18 years who presented with seizure for ≥5 min/actively convulsing to emergency were enrolled. END-IT score was calculated and correlated with outcome at discharge using Pediatric Overall Performance Category (POPC) scale, in-hospital mortality, and progression to refractory and super-refractory SE (SRSE). **Results:** We enrolled 140 children (mean age 5.8 years; 67.1% males). Seven children died and 15 had unfavorable outcomes. The predictive accuracy of END-IT at a cutoff of > 2: for unfavorable outcome (POPC score ≥3) was: sensitivity 0.73 (95% CI: 0.45–0.92), specificity 0.94 (95% CI: 0.89–0.98), PPV 0.61 (95% CI: 0.36–0.83), NPV 0.97 (95% CI: 0.92–0.99), positive likelihood ratio (13.09), F1 score (0.666); for death: sensitivity 0.86 (95% CI: 0.42–0.99), specificity 0.91 (95% CI: 0.85–0.95), PPV 0.33 (95% CI: 0.13–0.59), NPV 0.99 (95% CI: 0.96–1.00), F1 score (0.48); for RSE: sensitivity 0.80 (95%CI: 0.28–0.99), specificity 0.90 (95% CI: 0.83–0.94), PPV 0.22 (95% CI: 0.06–0.48) NPV 0.99 (95% CI: 0.96–1.00), F1 score (0.35); for SRSE: sensitivity 0.67 (95% CI: 0.22–0.96) specificity 0.75 (95% CI: 0.66–0.82), PPV 0.22 (95% CI: 0.06–0.48) NPV 0.98 (95% CI: 0.94–0.99), F1 score (0.33). **Conclusion:** We demonstrate utility of the END-IT score to predict short-term outcomes as well as progression to refractory and SRSE for the first time among children with SE.

Keywords: Epidemiology-based Mortality Score in Status Epilepticus, pediatrics, prognosis, refractory status epilepticus, Status Epilepticus Severity Score

Introduction

Status epilepticus (SE) is among the most common pediatric neurological emergencies, with an incidence ranging from 3 to 42 episodes/100,000 population per year.[1-3] Mortality following SE in children is estimated to be between 3 and 11%.[4] Often, SE provokes aggressive management, requiring intubation, mechanical ventilation, and the application of intravenous anesthetic agents. The risks and benefits of such an intensive approach remain debatable and must be balanced, since overtreatment may lead to iatrogenic complications and undertreatment to prolonged SE and neuronal damage.[5-10] An accurate estimation of the severity and prognosis of SE may vastly inform clinicians with respect to treatment optimization and intensification, as well as patients with SE and their families.

A number of scoring systems to predict outcomes in SE have been developed for adults including the Status Epilepticus Severity Score (STESS),[11,12] the Epidemiology-based Mortality Score in Status Epilepticus (EMSE),[13] the modified STESS (mSTESS),[14] and the Encephalitis Nonconvulsive status epilepticus Diazepam resistance Imaging Tracheal Intubation (END-IT) score.[15] Age is considered as a predictive variable in all of these scoring systems with the exception of the END-IT. However, none of these scoring systems have been applied among pediatric populations with SE so far.

Our group previously adapted the STESS score for use among the pediatric population by modifying the age component which we validated in a prospective study.[16] We found that this pediatric scoring system, STEPSS, was useful for predicting outcomes and treatment response among children with SE at a cutoff score >3. Recognizing the paucity of predictive scoring systems among children with SE, we further aimed to assess the usefulness of the END-IT score as a predictive tool among children with SE in the present study.

Methods

We conducted a retrospective cohort study at a tertiary care pediatric government hospital in New Delhi, India. We had earlier conducted a study evaluating a pediatric modification of the STESS score, the STEPSS (Status Epilepticus in Pediatric Patients Severity Score) to predict outcome and treatment response in children with SE.[16] We used the data collected in the STEPPS

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study and analyzed it for the present study. The methodology has been described earlier.[16] We enrolled children aged 1 month to 18 years who had presented with convulsive SE with seizure duration of at least 5 min or actively convulsing to the emergency services. We defined convulsive SE as per the International League Against Epilepsy (ILAE) operational definition[17] of seizure activity persisting beyond timepoint t1, defined as 5 min or more of convulsive seizures, or recurrent seizure activity without recovery of consciousness between seizures. The study was conducted between March 2016 and October 2018. Demographic data, history, examination findings, treatment details, clinical course during hospital stay and outcome were retrieved from the case records. The study was approved by the institutional ethics committee. Written informed consent was obtained from the parents/caregivers after the child had been stabilized initially. Approval from the ethics committee was obtained on 5.11.2016.

END-IT score

END-IT is an acronym for five predictor variables, namely: *E*ncephalitis, *N*on-convulsive status epilepticus (NCSE), *D*iazepam resistance, *I*mage abnormalities, and *T*racheal intubation.[15] Each of the five variables are assigned one point, with the exception of imaging abnormalities, in which unilateral lesions are scored one point and bilateral lesions or the presence of diffuse cerebral edema are scored two points. The outcome of SE can be estimated for an individual patient by summing the points of each variable, resulting in a total score ranging from 0 to 6. The probability of unfavorable outcome increases as the score increases [Table 1]. We defined "encephalitis" as per the definition provided by Indian consensus guidelines, as acute onset of fever with a change in mental status and/or new onset seizures, along with surrogate marker for central nervous system inflammation in cerebrospinal fluid or neuroimaging.[18] We made two modifications in the methodology compared to the original study: we used a cut-off of >5 min to define SE instead of >30 min, and we assessed only short-term outcomes at discharge, unlike the original paper which reported outcomes three months following discharge.

Evaluation of END-IT score

Details of history, examination, and investigations were extracted into a data sheet.[16] The enrolled children were treated as per standard hospital protocol which we have outlined earlier.[16] Response of the patients to antiseizure medications (ASMs) was noted. A patient was categorized to have benzodiazepine (BZD) responsive SE if he or she responded with the first or second BZD dose. Responsiveness was defined as SE ceasing within 10 min of initial administration of the medication and cessation of convulsion continuing for at least 30 min thereafter. Established SE was defined as SE which responded to second line ASM after BZD, usually phenytoin. Refractory SE (RSE) was defined as SE persisting despite the use of two appropriate ASMs (BZD and phenytoin) at acceptable doses and responding only to third line ASM or midazolam infusion. SRSE was defined as SE that continued 24 h or more after the introduction of the anesthetic agent, including those cases in which the SE recurred on reduction or withdrawal of anesthesia. The variables were extracted from the SE treatment charts, that is, (1) resistance to diazepam, coded as Yes or No and (2) tracheal intubation, coded as Yes or No. Neuroimaging findings were noted. According to the distribution of responsible lesions, brain images were classified into three different categories: no responsible lesion, unilateral responsible lesions, and bilateral responsible lesions or diffuse cerebral edema.

Imaging was done in patients with known epilepsy if they had persistent altered sensorium or developed super refractory status epilepticus.

We conducted 1 h electroencephalography (EEG) recording among all patients with RSE and SRSE, and patients with suspected non-convulsive status epilepticus. EEG was conducted in the EEG laboratory for stable patients and bedside EEG recording was done if the patient was unstable. The EEG was sampled at 256 Hz with a low frequency filter at 1 Hz and high frequency filter at 70 Hz. The scalp EEG was displayed in bipolar longitudinal. When clinically indicated, 1 h EEG recordings were repeated.

Table 1: Components of the END-IT Score

Relative factor	Categories	Points
Encephalitis	Yes	1
	No	0
Non-convulsive status epilepticus	Yes	1
	No	0
Diazepam resistance	Yes	1
	No	0
Imaging	Bilateral lesions/diffuse cerebral edema	2
	Unilateral lesion	1
	No responsible lesion	0
Tracheal intubation	Yes	1
	No	0

Outcome

The clinical outcome at the time of discharge was assessed using Pediatric Overall Performance Category (POPC) scale [Supplementary Table 1][19] POPC scale scores of 1–2 were considered as favorable outcome and scores of 3 and above were considered as unfavorable outcome. In children with pre-morbid developmental delay or disability, a return to baseline functional status was considered as favorable outcome, whereas a decline from baseline was considered as unfavorable. Baseline functional status was ascertained from parental history and previous medical documents. The primary outcome measure was the sensitivity of END-IT SCORE to predict an unfavorable outcome. We also studied other diagnostic utility parameters including specificity, negative (NPV) and positive predictive values (PPV). We also analyzed the utility of the END-IT score in predicting RSE and SRSE.

Statistical analysis

The data were entered into an EXCEL spreadsheet and analyzed using SPSS 16 [Chicago SPSS Inc.] and STATA

version 12. The predictive accuracy of END-IT score for favorable and unfavorable outcome was tested by calculating the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) at various cutoff points and their confidence intervals were determined by the Exact binomial method. The F1 scores were calculated to depict the balance between the positive predictive value and sensitivity. The receiver operating characteristic (ROC) curve was drawn and optimal cutoff point was determined by Youden's index (sensitivity + specificity -1) which gives equal importance to sensitivity and specificity. Youden's index of "1" indicates a "perfect" test and a value of "0" indicates that the test is useless.

Results

The demographic and the clinic-etiological profile of this cohort has already been described earlier.[16] We enrolled 140 children (94 boys) with mean age of 5.8 years (standard deviation 1.7 years). The median duration of seizures prior to presentation to hospital was 17.5 (Inter-quartile range [IQR] 15–20) min. Only 5.7% of the enrolled children had received treatment prior to coming to our hospital. Out of the enrolled children, 64 (47.1%) patients were known to have epilepsy, whereas 76 (52.9%) had the first episode of seizure presenting as status epilepticus. The demographic and clinical profile of the patients is detailed in Table 2.

Neuroimaging was done in 124 patients. It was not done in 16 because of rapid recovery/non affordability. These patients were hypocalcemic seizures (6) and febrile seizures (10). The clinical score for neuroimaging was given as 0 (normal) while calculating END-IT. Out of these 124 patients, 82 patients underwent CT and 42 underwent MRI.

END-IT scores in the study population

The END-IT score was applied in the study population. Sixteen (11.4%) patients had END-IT score >2. Of these, etiology of SE was acute meningoencephalitis in nine patients (viral), acute pyogenic meningitis in four patients, post-asphyxial cerebral palsy with epilepsy in two patients, and tubercular meningoencephalitis in one patient. Among these, 11 patients were intubated and non-convulsive status was observed in eight patients on bed-side EEG monitoring. MRI brain was normal in six patients and revealed unilateral lesions in five and bilateral lesions and/or cerebral edema in five patients.

Treatment response and outcome

Out of the 140 children enrolled, 117 (83.6%) were determined to be responsive to BZD. Established SE occurred in 12 (8.6%) children, 5 (3.6%) had RSE and 6 (4.3%) cases SRSE. Favorable outcomes occurred in 125 (89.3%) of the children and 15 (10.7%) had unfavorable outcomes. In our cohort, seven (5%) children died.

Predictive accuracy of the END-IT score

The END-IT score was found to be useful in predicting unfavorable outcome in children with status epilepticus [Table 3]. Youden's index (0.74) demonstrated that the END-IT score >2 was the optimal cutoff for the prediction of an unfavorable outcome [Table 4]. The predictive accuracy of END-IT at a cutoff of >2: for unfavorable outcome (POPC score ≥3) was as follows: sensitivity 0.73 (95% CI: 0.45–0.92), specificity 0.94 (95% CI: 0.89–0.98), PPV 0.61 (95% CI: 0.36–0.83), NPV 0.97 (95% CI: 0.92–0.99), positive likelihood ratio (13.09), F1 score (0.666); for death: sensitivity 0.86 (95% CI: 0.42–0.99), specificity 0.91 (95% CI: 0.85–0.95), PPV 0.33 (95% CI: 0.13–0.59), NPV 0.99 (95% CI: 0.96–1.00), F1 score (0.48); for RSE: sensitivity 0.80 (95%CI: 0.28–0.99), specificity 0.90 (95% CI: 0.83–0.94), PPV 0.22 (95% CI: 0.06–0.48) NPV 0.99 (95% CI: 0.96–1.00), F1 score (0.35); for SRSE: sensitivity 0.67 (95% CI: 0.22–0.96) specificity 0.75 (95% CI: 0.66–0.82), PPV 0.22 (95% CI: 0.06–0.48) NPV 0.98 (95% CI: 0.94–0.99), F1 score (0.33) [Table 4].

Discussion

In this retrospective cohort study, we evaluated the utility of a prognostic scale, the END-IT score, in childhood SE. We observed that a cutoff score of >2 on the END-IT predicted unfavorable outcomes including POPC scale scores at discharge, mortality, and progression to RSE and SRSE among children with SE. Thus far, with the exception of STEPSS, which our group has previously published, all other prognostic scores have been developed among adult populations with SE. Our cohort shared clinical and etiological characteristics

Table 2: Baseline characteristics of children enrolled (*n*=140)

Characteristics	*n* (%) or mean (SD)
Age (years)	5.8 (1.7)
Gender	
Male	94 (67.1)
Etiology	
Febrile seizure	26 (18.6)
Acute meningoencephalitis	15 (10.7)
Neurocysticercosis	12 (8.8)
Metabolic causes	9 (6.4)
Stroke	2 (1.4)
CNS tuberculoma	2 (1.4)
Hypertensive encephalopathy	1 (0.7)
Idiopathic	16 (11.4)
Post-asphyxial	18 (12.8)
Neonatal hypoglycemic brain injury	14 (10.0)
Post-encephalitic	13 (9.3)
Cerebral malformations	7 (5.0)
Primary generalised epilepsy	3 (2.1)
Dravet Syndrome	2 (1.4)
Co-morbidities	
Developmental delay	39 (27.9)
Cerebral Palsy	24 (17.1)
Vision/Hearing problems	10 (7.1)
Hyperactivity	2 (1.4)
Autism	1 (0.7)

CNS=Central nervous system

Table 3: Predictive accuracy of END-IT score for unfavourable outcome (POPC ≥3)

Total END-IT score	Sensitivity	Specificity	Positive likelihood ratio	Positive predictive value (%)	Negative predictive value (%)	Youden's index	F-1 Score
>0	0.93 (0.68-0.99)	0.61 (0.52-0.69)	2.38	0.22 (0.13-0.34)	0.99 (0.93-1.00)	0.54	0.359
>1	0.80 (0.52-0.96)	0.85 (0.77-0.91)	5.26	0.39 (0.22-0.58)	0.97 (0.92-0.99)	0.65	0.522
>2	0.73 (0.45-0.92)	0.94 (0.89-0.98)	13.09	0.61 (0.36-0.83)	0.97 (0.92-0.99)	0.68	0.666
>3	0.60 (0.32-0.84)	0.97 (0.92-0.99)	18.75	0.69 (0.39-0.91)	0.95 (0.90-0.98)	0.57	0.643
>4	0.47 (0.21-0.73)	0.99 (0.96-1.0)	58.38	0.88 (0.47-1.00)	0.94 (0.88-0.97)	0.46	0.609

Table 4: Predictive accuracy of END-IT score >2 for death and treatment response

Outcome	Sensitivity	Specificity	Positive likelihood ratio	Positive Predictive Value	Negative Predictive value	Youden's index	F1 score
Death	0.86 (0.42-0.99)	0.91 (0.85-0.95)	10.3	0.33 (0.13-0.59)	0.99 (0.96-1.00)	0.77	0.48
Refractory status epilepticus	0.80 (0.28-0.99)	0.90 (0.83-0.94)	7.69	0.22 (0.06-0.48)	0.99 (0.96-1.00)	0.70	0.35
Super-refractory status epilepticus	0.67 (0.22-0.96)	0.75 (0.66-0.82)	6.41	0.22 (0.06-0.48)	0.98 (0.94-0.99)	0.40	0.33

similar to other pediatric cohorts of SE described from developing countries.[20,21] Similar to these series, the most common cause of SE was acute symptomatic in nature in our study.

The END-IT was originally developed from a retrospective exploratory analysis as a prognostic score among patients with convulsive SE above the age of 12 years.[15] A cut-off point of 3 produced the highest sensitivity and specificity for functional outcome at 3 months post-discharge, considering demographic and clinical features, neuroimaging findings, and treatment responsiveness. Interestingly, unlike all the other prognostic scores for SE, age was not found to be a prognostic feature, and hence was not considered in the total score. This enabled us to employ the scale directly in a pediatric cohort, unlike our previous effort, STEPSS, wherein in we had modified the age component of the STESS score (≥65 and <65 years) to make it applicable to children (≥2 years and <2 years). Additionally, the median age group of the cohort on which the END-IT score was originally validated was 25.5 years (IQR, 17–48) years compared to the much older age range in STESS, EMSE, and mSTESS, suggesting that it was useful among younger patients with SE. This relatively young cohort was derived mainly from intensive care unit data, demonstrated prominence of encephalitis as a cause of SE, as well as the requirement for mechanical ventilation in many patients. Among patients with adult SE, these are not usually prominent features.[22] However, these very features facilitated application of the score in our pediatric cohort.

In the original study, using the cutoff value of a score of 3 or more, the END-IT score demonstrated sensitivity of 83.9%, specificity of 68.6%, PPV 70.3% with NPV of 82.8% for unfavorable functional outcomes at 3 months post-discharge, defined as modified Rankin score of 3–6.[15] We, however, used END-IT to predict functional outcome on discharge, which was a relatively short-term outcome, for which a score of >2, demonstrated sensitivity of 73%, specificity of 94%, PPV of 61%, and NPV of 97%.

Apart from functional outcome following discharge, END-IT has also been used in the prediction of in-hospital mortality. In our study, for the prediction of in-hospital death, a score of >2 demonstrated high NPV, making it a reliable predictor of patient survival. However, the low PPV in our study is similar to STESS as well as STEPSS, entailing that it cannot be used to withdraw support among children with SE based on a poor score.[13] In a retrospective comparative analysis on a cohort of 287 patients to assess in-hospital mortality, END-IT at a cutoff score of ≥3, had a sensitivity and specificity of around 64% which constituted a more balanced sensitivity-specificity ratio compared to STESS, mSTESS and EMSE.[6] However, END-IT did not perform better than the other scores despite requiring additional information in the form of etiological diagnosis, radiological features, and treatment response.[6] This was attributable to its younger population, with higher proportion of mechanically ventilated patients and nearly one-third patients harboring encephalitis as a cause of SE, features that are less frequent among adult patients with SE.[6,22] Moreover, the radiological features considered in the END-IT score did not differentiate between an acute and remote lesions. In another retrospective study, a combination of STESS and END-IT were used.[23] The study found that both STESS and END-IT were reliable predictors of in-hospital mortality among patients with SE, but END-IT was superior to STESS. The parallel combination of STESS and END-IT in which either scale being positive increased sensitivity (0.91) compared to compared to STESS alone ($P = 0.016$). In serial application with both scores being positive, improved specificity (0.95) was noted compared to either STESS or END-IT used alone ($P < 0.001$).

For predicting RSE and SRSE, a score of >2 demonstrated excellent NPV but poor PPV in our study, enabling prediction of which patients will not go on to develop these conditions. The END-IT has not been used in any other study for predicting evolution of SE to RSE or SRSE. In a retrospective analysis

of 177 patients with SE, the presence of encephalitis was observed to be the chief determinant of the progression from SE to SRSE.[24] However, further validation of the END-IT score among larger paediatric cohorts and multiple populations are required as a tool to predict progression to RSE/SRSE.

The advantages of the END-IT score are that it correlated well with both short-term outcomes as in our study, as well as functional status following discharge at 3 months, as in the original study. However, the END-IT cannot be applied directly at admission, as some information such as etiology, neuroimaging, and response to treatment may be available only later in the course of management.

Our study has several strengths. We have tested the utility of the END-IT score among children for the first time. We have tested the END-IT score in a reasonably large cohort of patients with complete short-term follow-up. Additionally, we have applied the scale to from diverse clinical settings, such as epilepsy clinics, emergency services, neurology inpatient facilities, and the intensive care units. This is in contrast to the original cohort, which was derived from data in the neurological intensive care unit setting. Additionally, we have employed the END-IT score in our study as a predictor tool for several short-term outcomes of interest in SE including discharge functional status, mortality during hospital stay, as well as the propensity for SE to convert to RSE and SRSE.

There were some limitations in our study. We certainly made some modifications in the original methodology described by Gao *et al*.: We employed the operational definition of convulsive status epilepticus to enrol children with persistent seizure activity beyond time point t1 (5 min) although the original definition used a cutoff of >30 min. Additionally, we assessed outcomes only at discharge, whereas the original study assessed outcomes at 3 months after discharge. Ours was a single-centre, hospital-based study. Data was obtained retrospectively. Additionally, we performed only short-duration EEG and in specific patients in whom NCSE was suspected or those who progressed to RSE or SRSE, considering resource constraints, which may not be optimal for NCSE detection. Neuroimaging was not done in 16 patients, which may have underestimated the END-IT score. Short-term outcomes, as measured by us using the POP-C scale, do not necessarily correlate with long-term outcomes. Cognitive and neurological sequelae are known to occur in patients with SE.[25] Although the END-IT score originally measured functional outcomes 3 months post-discharge, we employed it for short-term outcomes only. Thus, validity of these scores beyond the ICU discharge setting among children with SE needs to be established. Additionally, the number of patients with unfavorable outcomes is low in the present study and the study needs to be replicated in a larger cohort of patients.

In conclusion, we demonstrate the utility of the END-IT score as a prognostic tool to predict short-term outcomes as well as progression to refractory and super refractory status epilepticus among children with status epilepticus for the first time.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Supplemental Table 1: Pediatric Overall Performance Category (POPC) scale

Score	Category	Description
1	Good overall performance	Healthy, alert, and capable of normal activities of daily life
2	Mild overall disability	Possibility of minor physical problem that is still compatible with normal life; conscious and able to function independently
3	Moderate overall disability	Possibility of moderate disability from noncerebral systems dysfunction alone or with cerebral system dysfunction; conscious and performs independent activities of daily life but is disabled for competitive performance in school
4	Severe overall disability	Possibility of severe disability from noncerebral systems dysfunction alone or with cerebral system dysfunction; conscious but dependent on others for activities of daily living support
5	Coma or vegetative state	
6	Brain death/death	