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Status Epilepticus in Pediatric patients Severity Score (STEPSS): A clinical score to predict the outcome of status epilepticus in children- a prospective cohort study

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ABSTRACT

Purpose: In adults, the Status Epilepticus Severity Score (STESS), a clinical score, has been shown to be a good predictor of outcome and treatment response. We devised a pediatric modification of this score: the Status Epilepticus in Pediatric patients Severity Score (STEPSS) and evaluated it in children with status epilepticus.
Methods: In this prospective study, children aged 1 month to 18 years presenting with seizure duration ≥ 5 min or actively convulsing to the emergency room were enrolled. STEPSS score was calculated at the time of admission. Outcomes included death, the Pediatric Overall Performance Category (POPC) at discharge and treatment response. The diagnostic utility of the STEPSS score to predict unfavourable outcome was evaluated.
Results: One-hundred and forty children (mean age 5.8 years) were enrolled. Seven children died and overall 15 children had an unfavourable outcome. The predictive accuracy of STEPSS at a cut-off of > 3: for unfavourable outcome (POPC score ≥ 3) - sensitivity (0.93 [95% CI: 68, 99.8]), specificity (0.81 [95% CI: 0.73, 0.87]), PPV (0.37 [95% CI: 0.22, 0.54]), NPV (0.99 [95% CI: 0.95–1.0]), positive likelihood ratio (4.86), F1 score (0.530); for death - sensitivity (0.86 [95% CI: 0.42, 0.99]), specificity (0.76 [95% CI: 0.68-0.83]), PPV (0.16 [95% CI: 0.06, 0.31]), NPV (0.99 [95% CI: 0.95, 1.0]), F1 score (0.270).
Conclusions: The STEPSS, a simple bedside clinical score, was found to be useful to predict the outcome and treatment response in children with status epilepticus.

1. Introduction

Status epilepticus (SE) is a frequent neurological emergency with short term mortality ranging from 0.9 to 3.6% in children [1–5]. The outcome of status epilepticus is determined mainly by the underlying etiology, delays in treatment and the refractoriness of the ongoing seizures to treatment [6–10]. The morbidity of status epilepticus increases as the seizure becomes refractory to medical therapy. Identifying the clinical factors that predict the outcome of patients with status epilepticus is important as this may be useful for deciding further treatment. The use of a severity scale at baseline may help to tailor therapies and can be used for research purposes as well.

In adults, various scores have been developed to predict the outcome in cases of SE. One of these is the Status Epilepticus Severity Score (STESS) which is based on baseline clinical parameters such as age, level of consciousness, type of seizure and whether the patient has a past history of seizures [11]. This scale has been shown to be a good predictor of mortality and of need for aggressive treatment [12,13]. Currently, there is no score available for predicting the outcome of SE in children. In this study, we planned to evaluate a baseline clinical score for prediction of short term outcome of SE in children in a prospective cohort study. This clinical score was a modified version of STESS for

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pediatric patients- the **St**atus **E**pilepticus in **P**ediatric patients **S**everity **S**core (STEPSS). The objective of this study was to evaluate the predictive accuracy of STEPSS to predict the short term outcome of SE in children.

2. Methods

This was a prospective, cohort study carried out at a tertiary care, government-sponsored pediatric hospital in New Delhi, India from October 2016 to March 2018. This is one of the major referral pediatric hospital in north India and receives patients from Delhi and surrounding states. Children aged 1 month to 18 years presenting with seizure duration of at least 5 min or actively convulsing to the emergency room, were enrolled. Approval from the institutional ethics committee was obtained. Written informed consent was taken from the parents/caregivers after initial stabilization of the child.

2.1. STESS score and its pediatric modification STEPSS

STESS is a simple bedside assessment score (range 0–6) which is calculated from 4 clinical variables- age of the patient, level of consciousness, past history of seizures, and type of Status Epilepticus (Table 1) [11]. A lower score indicates a less severe presentation and vice versa. At a cutoff of ≥3 (score 2), the predictive validity for mortality included sensitivity, 1.000; specificity, 0.643; and negative predictive value, 1.000 in adults with status epilepticus [11].

In STESS, for the age criteria, 0 points are given if the age is < 65 years of age, and 2 points are given if the age is ≥ 65 years (Table 1). As the age criteria was unsuitable for use in pediatric population, we reviewed the literature on what age cut off should be used in children. We modified the age criteria to < 2 years of age to yield 2 points, and ≥ 2years to yield 0 points in the pediatric modification, STEPSS (Table 1). This modification was based on review of previously available literature on prognostic factors of SE in children; children less than 2 years of age were found to have increased risk of mortality [14]. The rest of the criteria of STESS score were retained as it were.

2.2. Evaluation of STEPSS score

The parameters for the STEPSS score were noted at the time of presentation in the emergency room. The level of consciousness was noted prior to benzodiazepine administration. To avoid bias, the treating team was blinded to the STEPSS score at presentation.

2.3. Procedure

Detailed history, examination and investigations were documented in a data extraction sheet. The etiology of SE was determined according to the history, examination and the investigations done. The enrolled children were treated as per the standard hospital protocol (Fig. 1). The anti-seizure medications (ASM) was considered effective if there was cessation of SE within 10 min of the initial dose of medication and if there was a sustained absence of convulsions for 30 min. Response of the patients to the ASMs was also noted. A patient was classified to have Benzodiazepine responsive SE if the SE responded with first or second dose of BZD. Established SE was defined as SE which responded to the second line ASM after BZD, usually phenytoin. Refractory SE was defined as SE persisting despite the administration of two appropriate anticonvulsants (BZD and phenytoin) at acceptable doses and responding only to third line ASM or midazolam infusion. Super-refractory SE was defined as SE that continued 24 h or more even after the onset of anesthesia, including those cases in which the SE recurred on the reduction or withdrawal of anesthesia. The patients were followed till discharge or death.

One-hour EEG was done in all patients with refractory and super-refractory SE, and patients with suspected non-convulsive status epilepticus, absence and myoclonic SE. This was done in the EEG lab if the

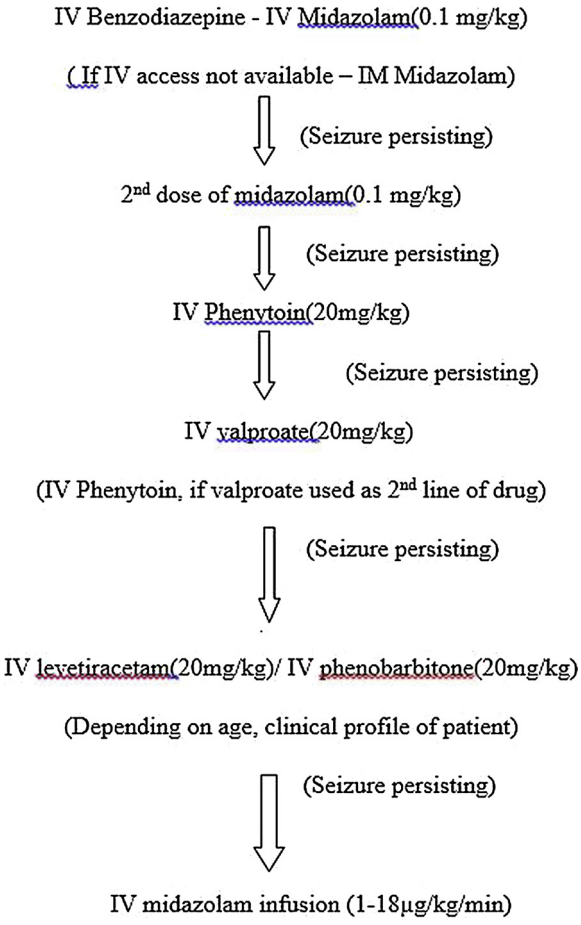

Fig. 1. Hospital Protocol for the treatment of Status epilepticus.

Table 1
Status Epilepticus Severity Score (STESS) and its modification Status Epilepticus in Pediatric patients Severity Score (STEPSS).

Features Score	Status Epilepticus Severity Score (STESS)		Status Epilepticus in Pediatric patients Severity Score (STEPSS)	
Consciousness	Alert or somnolent/confused	0	Alert or somnolent/confused	0
	Stuporous or comatose	1	Stuporous or comatose	1
Worst seizure type	Simple-partial,Complex partial, absence, myoclonic	0	Simple-partial,Complex partial, absence, myoclonic	0
	Generalised-convulsive	1	Generalised-convulsive	1
	Non-convulsive,status epilepticus in coma	2	Non-convulsive,status epilepticus in coma	2
Age	< 65 years	0	**≥2 years**	0
	≥65 years	2	**< 2 years**	2
History of previous seizures	Yes	0	Yes	0
	No or unknown	1	No or unknown	1
TOTAL		0-6		0-6

Table 2
Components of the STEPSS score in the study population (N = 140).

Features	Score		N (%)
Consciousness	Alert or somlonent/confused	0	78(55.7)
	Stuporous or comatose	1	62(44.3)
Worst seizure type	Simple-partial, Complex partial, absence, myoclonic	0	30(21.4)
	Generalised-convulsive	1	106(75.7)
	Non convulsive status epilepticus in coma	2	4(2.9)
Age	≥2 years	0	84(60.0)
	< 2 years	2	56(40.0)
History of previous seizures	Yes	0	84(60.0)
	No or unknown	1	56(40.0)

patient was stable, and bedside, if the patient was unstable and could not be transported to the EEG lab. EEG was available only during the working hours. Twenty- one channels were recorded, including the 19 standard scalp electrodes, referenced to Pz. 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 then displayed in a bipolar antero-posterior montage. EEG was repeated as per the clinical indications (Table 2).

2.4. Outcomes

All patients were classified using the Pediatric Overall Performance Category (POPC) scale at the time of discharge from the hospital (Supplemental Table 1) [15]. POPC scale scores of 1 or 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 their baseline functional status was considered as favourable outcome, a decline from before was considered as unfavorable. Pre-morbid disability score was assessed by using an estimated POPC scale by asking the parents about the baseline functional status and by reviewing the previous medical records, where available. The primary outcome measure was the sensitivity of the STEPSS to predict an unfavourable outcome. We also studied the other diagnostic utility parameters such as specificity, negative (NPV) and positive predictive values (PPV). We also analysed the utility of the STEPSS to predict refractory and super-refractory status epilepticus.

2.5. Statistical analysis

The expected sensitivity was 90% based on the data of adult patients evaluated with STESS. With a precision of 10% on either the side and with confidence level of 95%, 35 patients with unfavourable outcome were required; expecting 25% proportion of unfavourable patients, a total of 140 patients were needed for the this study. The sample size was also determined for 90% specificity with 10% precision which is less than 140. Data was entered in EXCEL sheet and analysed using SPSS -16 [Chicago SPSS Inc.] and STATA version 12. Data was presented as means, standard deviations and proportions with percentages. The predictive accuracy of STEPSS for death, unfavourable outcome and development of refractory and super-refractory status epilepticus was tested by calculating the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) at various cut-off 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. A score of 1 reflects the best possible balance and 0 the worst. The receiver operating characteristic (ROC) curve was drawn and optimal cut-off 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.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline in this manuscript.

3. Results

3.1. Demographic and clinico-etiological profile

A total of 140 children (94 boys) with a mean age of 5.8 years (standard deviation, 1.7 years) were enrolled in the study (Supplemental Fig. 1). The approximate median duration of seizures prior to presentation (based on parental report) to hospital was 17.5 min (Inter-quartile range: 15–20 min). Only 5.7% of the enrolled children had received treatment prior to coming to the hospital. Out of the enrolled children, 47.1% patients were known cases of epilepsy whereas 52.9% had the first episode of seizure presenting as status epilepticus. The co-morbidities included developmental delay/intellectual disability (27.9%), cerebral palsy (17.1%), and vision/hearing impairment (7.1%), hyperactivity (1.4%) and autism spectrum disorder (0.7%).

The most common etiology was acute symptomatic which was present in 36 patients (25.7%), followed by remote symptomatic which was present in 35(25%) patients. Febrile status epilepticus was present in 26 patients (18.6%). Metabolic causes (hypocalcemia/ hypoglycaemia) of seizures presenting as status epilepticus were present in 9(6.4%) of patients. Neurocysticercosis was found to be cause of status epilepticus in 12(8.6%) patients.

3.2. STEPSS Scores in the study population

The STEPSS was applied in the study population (Table 4). Seventy-eight (55.7%) of patients were either alert or somnolent/confused at the time of presentation while 62(44.3%) were stuporous or comatose. Amongst type of seizure, generalized tonic clonic seizure was most common type being present in 106(75.7%) followed by complex partial/focal impaired awareness (22), simple partial/focal aware (5), absence (2) and myoclonic seizures (1). Four (2.9%) patients presented in non-convulsive status epilepticus (all had focal electrographic seizures).

3.3. Treatment response and outcome

Out of the enrolled children, 117(83.6%) patients were BZD responsive, 12(8.6%) had established status epilepticus, i.e. unresponsive to BZD but responsive to phenytoin, 5(3.6%) had refractory status epilepticus, i.e. unresponsive to BZD and phenytoin while 6(4.3%) cases had super refractory status epilepticus. Seven children (5%) died. Overall, 125 (89.3%) children had a favourable outcome and 15 (10.7%) children had an unfavourable outcome.

3.4. Predictive accuracy of the STEPSS

The ROC curve (area under the curve 0.95 [95% CI:0.91-0.99]) suggested that STEPSS score was very useful in predicting unfavourable outcome in children with status epilepticus (Fig. 2). Youden's index (0.74) demonstrated that STEPSS score of > 3 was the optimal cut-off for the prediction of an unfavourable outcome (Table 3).

The predictive accuracy of STEPSS at a cut-off of > 3: for unfavourable outcome (POPC score ≥ 3) - sensitivity (0.93 [95% CI: 68, 99.8]), specificity (0.81 [95% CI: 0.73, 0.87]), PPV (0.37 [95% CI: 0.22, 0.54]), NPV (0.99 [95% CI: 0.95–1.0]), positive likelihood ratio (4.86), and F1 score (0.530). The accuracy parameters for death, refractory status epilepticus, and super-refractory status epilepticus – are summarized in Table 4. The F1 score, which reflects a balance and trade-off between positive predictive value and sensitivity was the best (0.530) for unfavorable outcome at a STEPPS cut-off of > 3 and the worst for super-refractory status epilepticus (0.190).

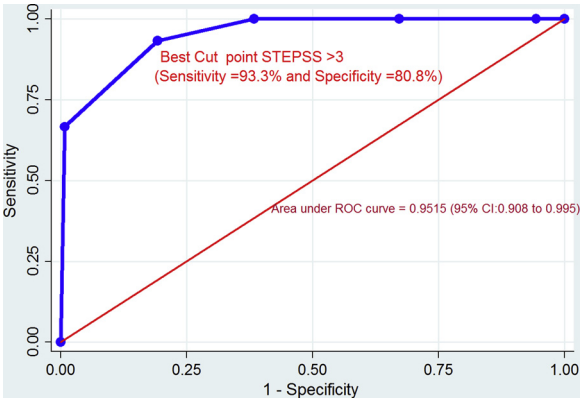

Fig. 2. Receiver Operating Characteristic (ROC) Curve of STEPSS Score for unfavourable outcome.

4. Discussion

In this prospective cohort study, we evaluated a clinical status epilepticus severity score, the STEPSS, to predict the outcome and treatment response. STEPSS, at a cut-off of > 3, was found to have a good predictive accuracy for unfavourable outcome at time of discharge, death and treatment response (occurrence of refractory and super-refractory status epilepticus) in our population.

The demographic and clinic-etiological profile of our study population was similar to other studies on pediatric status epilepticus from developing countries, with acute symptomatic etiology being the most common cause. The mortality rate was 5%, lower than 10–30% reported mortality in adult patients. However, this is comparable to other studies on childhood status epilepticus. In a recent retrospective study on 610 children with status epilepticus, the authors reported mortality in 4.6% of the cases [16]. Children with status epilepticus overall have better outcomes than adults, likely because of the presence of relatively benign causes such as febrile status epilepticus and underlying epilepsy compared to adults in whom acute symptomatic causes such as stroke and central nervous systems are common. Another reason could also be that most of the older adult status epilepticus studies have used the 30 min duration definition of status epilepticus while we have used the operational 5 min definition.

The STESS was developed in 2006 as a simple clinical bedside tool to be performed at the time of presentation to predict the outcome and treatment response of status epilepticus in adults [11]. In the original study, the authors reported sensitivity 1.000; specificity, 0.643; negative predictive value, 1.000; and unweighted accuracy, 0.822 and the optimal cutoff was ≥3 [11]. Since then, several studies have evaluated STESS in status epilepticus in adults and have reported similar results [12,13,17–24].

Recently, Wang et al reported the results of a meta-analysis to evaluate the diagnostic accuracy of STESS for survival [25]. A total of 11 studies including 12 observations with 1356 patients were included. Summary estimates of the diagnostic value of STESS for patient survival demonstrated sensitivity of 81% and specificity of 53% with area under the curve (AUC), 0.81. Meta-regression analysis showed that ethnicity, study design, publish year, and sample size did not significantly influence the diagnostic performance of STESS.

The present study is the first study evaluating a clinical status epilepticus severity score in children. We evaluated a pediatric modification of STESS, i.e. STEPSS for predicting the outcome. The STEPSS score with cut off > 3 showed 0.93 sensitivity and 0.81 specificity in predicting the unfavourable outcome with PPV of 0.37 and NPV of 0.99. STEPSS score > 3 predicted death as outcome with 0.86 sensitivity and 0.76 specificity with PPV of 0.16 and NPV of 0.99. The results were comparable to adult studies on STESS (Supplemental Table 2) [11–1317–24].

For predicting treatment response, the STEPSS score of > 3, had 0.82 sensitivity, 0.78 specificity, 0.24 PPV and 0.98 NPV for the development of refractory status epilepticus while for predicting the development of super refractory seizures STEPSS score > 3 had 0.67 sensitivity, 0.75 specificity, 0.11 PPV, 0.98 NPV. In a study by Goyal et al, STESS score < 3 had PPV of 83.3% for predicting control of seizures with in 1 h. STESS score of < 2 had NPV of 87% for control of SE within 1 h of treatment [12].

In all reported studies the STESS has been reported to have an excellent negative predictive value (97%–99%) [11–1317–24]. A favourable STESS has been found to be highly associated with survival and return to baseline clinical status. We also found a very high negative predictive value of STEPSS in our study.

Other status epilepticus predictive scores which have been developed include the epidemiology-based mortality score (EMSE) [24] and the Encephalitis Nonconvulsive Status Epilepticus Diazepam Resistence Imaging Tracheal Intubation (END-IT) score [26]. Out of these, both EMSE and the END-IT score use the parameter of etiology, which is not always known at presentation and needs investigations. The STESS and its pediatric modification STEPSS have the advantage that they can be done at presentation, are based on clinical parameters, and hence can be used to guide treatment and for prognostication.

The strengths of this study include a prospective design, a good sample size and adequate follow-up to determine the short term outcomes of status epilepticus in children. The limitations include inability to study long term outcomes and hospital-based study design. Further, the etiology of status epilepticus may differ in other populations and therefore, the generalizability of the study results may be limited. The score need to be evaluated in other pediatric populations in other settings to better validate the results. It would have been ideal to have an EEG done at arrival to the emergency room, however this was not possible in our resource-constraint setting. Also, the non-availability of continuous EEG monitoring had limited our ability to diagnose non-convulsive status epilepticus. These would have affected the STEPSS scoring.

In conclusion, we modified a clinical status epilepticus severity score STESS for pediatric use; the STEPSS, and evaluated it in a prospective cohort of children (from north India) with status epilepticus. The STEPSS was found to be useful to predict the outcome (death and functional outcome) and treatment response. Further studies in larger cohorts are needed to confirm the predictive validity of STEPSS in children with status epilepticus.

Table 3
Predictive accuracy of STEPSS for unfavourable outcome (POPC ≥ 3).

Total STEPSS score	Sensitivity	Specificity	Positive likelihood ratio	Positive predictive value (%)	Negative Predictive value (%)	Youden's index	F 1 Score
> 0	1.00 (0.78-1.0)	0.056 (0.02-0.11)	1.059	0.11 (0.07-0.18)	1.00 (0.97-1.0)	0.06	0.198
> 1	1.00 (0.78-1.0)	0.33 (0.25-0.42)	1.488	0.15 (0.09-0.24)	1.00 (0.97-1.0)	0.33	0.261
> 2	1.00 (0.78-1.0)	0.62 (0.53 -0.71)	2.604	0.24 (0.14-0.36)	1.00 (0.97-1.0)	0.62	0.387
> 3	**0.933(0.68-0.99)**	**0.81 (0.73 – 0.87)**	**4.859**	**0.37 (0.22-0.54)**	**0.99 (0.95-0.99)**	**0.74**	**0.530**
> 4	0.67(0.38-0.88)	0.96 (0.91-1.0)	17.103	0.91 (0.59-0.99)	0.96 (0.91-0.99)	0.63	0.772

Table 4
Predictive accuracy of STEPSS score > 3 for death and treatment response.

Outcome	Sensitivity	Specificity	Positive likelihood ratio	Positive Predictive Value	Negative Predictive value	F1 score
Death	0.86 (0.42-0.99)	0.76 (0.68-0.83)	3.556	0.16 (0.06-0.31)	0.99 (0.46-0.99)	0.270
Refractory status epilepticus	0.82 (0.48-0.98)	0.78 (0.69-0.84)	3.636	0.24 (0.11-0.40)	0.98 (0.93-0.99)	0.371
Super-refractory status epilepticus	0.67 (0.22-0.96)	0.75 (0.66-0.82)	2.626	0.11 (0.03-0.25)	0.98 (0.93-0.99)	0.190

Funding

None.

Ethics

The study was approved by the research ethics board of the hospital.

Declaration of Competing Interest

None for all the authors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.09.005.

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