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Original Article

Status Epilepticus in Pediatric patients Severity Score (STEPSS) as an outcome predictor in children

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Abstract

Background Status epilepticus (SE) is a neurological emergency, with short-term mortality ranging from 0.9 to 3.6% in children. The disease burden of SE includes morbidity, treatment costs, and mortality. Various scoring tools for predicting outcomes in adult SE cases have been widely studied, but there are few tools for predicting outcomes in children with SE.

Objective To evaluate the usefulness of *Status Epilepticus in Pediatric patients Severity Score* (STEPSS), a clinical score for predicting functional outcomes and mortality in pediatric patients with status epilepticus, as well as to identify characteristics of SE patients.

Methods This retrospective cohort study included 88 pediatric patients with status epilepticus aged >1 month to ≤18 years by consecutive sampling, who were treated at Dr. Sardjito Hospital, Yogyakarta. All subjects underwent assessment by STEPSS, which were compared to functional outcomes assessed by *Pediatric Overall Performance Capacity* (POPC) score and mortality.

Results STEPSS > 3 was significantly correlated with poor functional outcomes (OR 2.85; 95%CI 1.04 to 7.87; P=0.043), but was not significantly correlated with mortality outcome in children with SE (P=0.411).

Conclusion *Status Epilepticus in Pediatric patients Severity Score* (STEPSS) with cut-off >3 can be used as a predictor of poor functional outcomes in pediatric patients with SE aged >1 month to ≤18 years, but cannot be used as a predictor of mortality. **[Paediatr Indones. 2022;62:396-403; DOI: https://doi.org/10.14238/pi62.6.2022.396-403**].

Keywords: *STEPSS; status epilepticus; functional outcome; mortality*

Status epilepticus (SE) is a common neurological emergency, with short-term mortality ranging from 0.9 to 3.6% in children. The outcomes of SE patients are primarily related to underlying etiology, delay in treatment, and ongoing refractory seizures during treatment. The morbidity of SE increases with the occurrence of seizures that are refractory to the given medical therapy. According to a systematic review, the mortality rate for convulsive status epilepticus (CSE) varies from 7.6 to 39% in population-based studies.[1]

In a London study of 176 children who had an episode of status epilepticus, 62-84% had their first seizure. The incidence of SE is 17-23 episodes per 100,000 per year. Approximately 56% of children were neurologically healthy before the first episode of SE and 57% of these children had prolonged febrile seizures. The estimated recurrence of CSE over 1 year is 16% (10-24%), while case fatality is 3% (2-7%).[2]

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In developing countries such as India, the child mortality rate due to SE was 4-6%, lower than the adult mortality rate of 10-30%.[3]

Various tools to predict outcomes in SE cases have been developed, especially for adult SE patients. The first study to examine clinical score to predict the prognosis of adult SE patients was known as the *Status Epilepticus Severity Score* (STESS). This STESS is a clinical score consisting of four variables, namely, awareness, type of seizure, age at onset, history of seizures. This score is used as a prognostic tool to predict the survival of SE patients and their risk of death, by observing SE patients during hospitalization until discharge. The STESS as a useful tool for determining rational planning at the level of monitoring and modulating aggressive management. Subsequent studies on STESS using clinical parameters in accordance with previous studies, were applied to adult SE patients. This scale has been shown to be a good predictor of mortality and the need for aggressive treatment.[4,5]

Status Epilepticus in Pediatric patients Severity Score (STEPSS) is useful for predicting mortality, functional outcome, and treatment response.[3] A study in Northern India modified the STESS clinical score in adults for use in children with SE. In our study, we also modified STESS to the *Status Epilepticus in Pediatric patient Severity Score* (STEPSS), by changing one of the variables in the STESS score, namely, age and evaluating it in a prospective group of children with SE.

Methods

This cohort retrospective study was conducted at Dr. Sardjito Hospital, Yogyakarta, Indonesia, from January 2017 to March 2021. The inclusion criteria were children aged >1 month to ≤18 years who were diagnosed with status epilepticus, regardless of the etiology, and were treated at Dr. Sardjito Hospital, Yogyakarta, Central Java. Status epilepticus was defined as seizures that last continuously for a certain period of time, or recur without being accompanied by a return of consciousness between seizures. Children were included by consecutive sampling, retrospectively using medical record tracing which was noted on the case report form (CRF). All 88 subjects' functional outcomes and mortality status at the time of discharge from the hospital were noted.

STEPSS (**Table1**),[3] *Pediatric Overall Performance Capacity* (POPC) scores (**Table 2**),[3] and *Pediatric Comorbidity Index* (PCI) scores (**Table 3**)[6] were determined by independent data collectors (medical students in clinical year). The STEPSS was a clinical score to predict the outcome of pediatric patient with SE, STEPSS with a cut off >3 had a sensitivity of 93% and specificity of 81% for poor outcomes. While POPC was a global score to determine functional outcomes based on observations (cut off score ≥3 indicated a poor outcome).[3] The PCI was a score used to determine the degree of comorbidity in pediatric cancer patient. Application of this index in the hospitalized patient population was very useful for a clinical evaluation and decision making during clinical follow up.

Subjects were assessed for STEPSS based on medical record data; subjects' functional outcomes and mortality were noted. Functional outcomes were measured by changing the POPC score before the SE episode with the POPC score at the time of discharge from the hospital. The mortality outcome used in this study was either survived or died during hospitalization.

Secondary research data obtained from medical records were processed using the *Statistical Package for the Social Science (SPSS) version 25* software. Patient characteristics on normally distributed data were presented in terms of mean and standard deviation and those on a categorical scale were presented in numbers and percentages. The total STEPSS was then grouped based on the cut-off (≤3 and >3) based on North Indian study.[3] Bivariate analysis was done with Chi-square test (if there were no cells with expected values <5) or Fisher's exact test (if there were cells with expected values <5). The independent and external variables with P values <0.25 in the bivariate analysis were analyzed by multivariate logistic regression. This study had a 95% confidence level or 5% alpha. The study was approved by the Health Research Ethics Committee of the Medical Faculty of Gadjah Mada University.

Table 1. *Status Epilepticus in Pediatric patients Severity Score* (STEPSS)[3]

Variables	Score
Consciousness	
Alert or somnolent or confused	0
Stupor or coma	1
Type of seizures	
Simple partial, complex partial, myoclonic, absence	0
Generalized convulsive	1
Non-convulsive SE, in coma	2
Age, years	
<2	0
≥2	2
Past history of seizures	
Yes	0
No/unknown	1
	(0-6)

Table 2. *Pediatric Overall Performance Capacity* (POPC) score[3]

Score	Category	Description
1	Normal, overall good function and good performance (able to carry out normal daily activity)	Alert and capable of normal activities of daily living
2	Mild disabilities	Minor disabilities are possible; minor physical problems that are still compatible with normal life
3	Moderate disabilities	From possible defect of non-brain system causing dysfunction or with aberration of cerebral function; independent in activities of daily living, but disabled; competitive performance in school
4	Severe disability	Severe disability from non-brain system dysfunction or with brain dysfunction; conscious but dependent on others for daily life activities
5	Vegetative state or coma	
6	Death (brain death)	

Table 3. *Pediatric Comorbidity Index* (PCI)[6]

Disease	Score	Disease	Score
Pneumonia	1	Coagulopathy	1
Septicemia	1	Heart failure	4
Malnutrition	2	Obesity	1
Shock	4	Congenital heart disease	2
HIV/AIDS	4	Arrythmia	1
Leukemia	4	Genetic syndrome	4
Brain cancer	4	Short stature	1
Hydrocephalus	1	Brain injury due to trauma	2
Hypertension	2	Diabetes insipidus	4
Acute kidney failure	2	Cerebrovascular events	2
Candidiasis	2	TOTAL SCORE:	

Results

Baseline characteristics of subjects are shown in **Table 4**. There were equal numbers of male and female subjects. Subjects' median age was 2.5 (range 0.83-9.34) years, with 44.3% were younger than 2 years of age and 55.7% were older than 2 years of age. Seventy-six (86.4%) subjects had generalized tonic clonic (GTC) seizures, while 12 (13.6%) had focal/partial seizures. Fifty-five (62.5%) patients had no previous history of seizures, while 33 (37.5%) patients had a previous history of seizures. STEPSS distribution was >3 in 27 (30.7%) and STEPSS ≤3 in 61 (69.3%). Comorbidities assessed by the PCI revealed score ≥6 (high comorbidity) in 22 (25%) subjects and <6 (low comorbidity) in 66 (75%) subjects. Etiologies were classified as infectious in 40 (45.5%) and non-infectious in 48 (54.5%).

Functional and mortality outcomes were noted. Functional outcomes were assessed based on change in the POPC score from before the SE episode to that at the time of hospital discharge. An increase in POPC indicated poor functional outcome, while stable POPC score indicated good functional outcomes. Of our 88 subjects, 48 (54.5%) had poor and 40 (45.5%) had good functional outcomes. Sixteen (18.2%) subjects died and 72 (81.8%) survived (**Table 4**).

Significantly more SE patients with STEPSS >3 had poor functional outcomes than those with a STEPSS of ≤ 3 (OR 2.85; 95%CI 1.04 to 7.87; P=0.043). Comorbidity (P=0.323) and etiology (P=0.072) were not significantly different between good and poor functional outcome groups (**Table 5**).

Subjects with high comorbidities (PCI score ≥6) had significantly higher mortality outcomes than those with low comorbidities (OR 5.53; 95%CI 1.55 to 19.65; P=0.008). STEPSS (P=0.411) and etiology (P=0.063) were not significantly different between mortality outcome groups (**Table 6**).

Table 4. Characteristics of subjects (N=88)

Characteristics	n (%)	POPC			Mortality		
		Increased score (n=48)	Stable score (n=40)	P value	Died (n=16)	Survived (n=72)	P value
Age, n(%)							
< 2 years	39 (44.3)	24 (61.5)	15 (38.5)	0.24	9	30 (76.9)	0.28
≥ 2 years	49 (55.7)	24 (49.0)	25 (51.0)		7	42 (85.7)	
Sex, n(%)							
Male	44 (50.0)	26 (59.1)	18 (40.9)	0.39	6	38 (86.4)	0.26
Female	44 (50.0)	22 (50.0)	22 (50.0)		10		
Consciousness, n(%)							
Stupor	38 (43.2)	27 (71.1)	11 (28.9)	0.007	10	28 (73.7)	0.08
Somnolence	50 (56.8)	21 (42.0)	29 (58.0)		6	44 (88)	
Seizure type, n(%)							
GTC	76 (86.4)	41 (53.9)	35 (46.1)	0.777	15	61 (80.3)	0.68
Partial	12 (13.6)	7 (58.3)	5 (41.7)		1	11 (91.7)	
Seizure history, n(%)							
No	55 (62.5)	37 (67.3)	18 (32.7)	0.002	4	41 (74.5)	0.02
Yes	33 (37.5)	11 (33.3)	22 (66.7)		2	31 (93.9)	
STEPSS, n(%)							
>3	27 (30.7)	19 (70.4)	8 (29.6)	0.047	7	20 (74.1)	0.24
≤3	61 (69.3)	29 (47.5)	32 (52.5)		9	52 (85.2)	
PCI score, n(%)							
≥6	22 (25.0)	14 (63.6)	8 (36.4)	0.323	8	14 (63.6)	0.02
<6	66 (75.0)						
Etiology, n(%)							
Infectious	40 (45.5)	26 (65.0)	14 (35.0)	0.072	10	30 (75.0)	0.13
Non-infectious	48 (54.5)	22 (45.8)	26 (54.2)		6	42 (87.5)	

Table 5. Bivariate and multivariate analyses of functional outcomes

Variables	Bivariate analysis			Multivariate analysis		
	RR	95%CI	P value	OR	95%CI	P value
STEPSS						0.043
>3	1.48	1.03 to 2.12	0.047	2.85	1.04 to 7.87	
PCI score						
≥6	1.24	0.83 to 1.83	0.323			
Etiology						0.129
Infectious	1.42	0.97 to 2.08	0.072	1.99	0.82 to 4.84	

Table 6. Bivariate and multivariate analyses of mortality outcomes

Variables	Bivariate analysis			Multivariate analysis		
	RR	95%CI	P value	OR	95%CI	P value
STEPSS						
>3	0.239	1.76 to 4.23	0.73	1.66	0.49 to 5.54	0.411
PCI score						
≥6	3.00	1.28 to 7.04	0.022	5.53	1.55 to 19.65	0.008
Etiology	2.00	0.79 to 5.02	0.130	3.31	0.94 to 11.73	0.063
Infectious						

Discussion

In this retrospective cohort study, we evaluated STEPSS to predict functional and mortality outcomes of SE in children. Multivariate analysis of functional outcomes assessed by POPC score change revealed that significantly more SE patients with STEPSS >3 had poor functional outcomes compared to subjects with STEPSS ≤3 (P=0.043). SE patients with a STEPSS >3 had a 2.85 times higher risk of experiencing a poor functional outcome compared to a STEPSS of <3 (95%CI 1.04 to 7.87).

Patients who survive SE are at risk for long-term neurological disability, including focal neurological deficits, namely diplegia, extrapyramidal syndrome, cerebellar syndrome, cognitive impairment, seizure recurrence or epilepsy, and behavioral problems.[9] Consistent with previous studies, SE patients were at risk of poor functional outcome, in which SE patients had elevated POPC (poor functional outcome) compared to stable POPC changes.[3,4]

Neurologic complication rates in children with SE were reported to be 29% among infants less than 1 year of age, 11% in children 1-3 years of age, and 6% among children aged >3 years.[7] A Canadian study in children with convulsive SE showed that the condition was independently associated with significantly poorer quality of life, in terms of health and several functional domains, including physical function, social and emotional well-being, behavior, and cognition.[8]

Predictive accuracy of cut-off STEPSS >3 for predicting undesirable outcomes, according to (POPC≥3 score).[3] Our results were in agreement with those of previous studies that suggested STEPSS cut-off >3 would be a useful predictor of functional outcomes in SE patients who were evaluated with POPC.

Comorbidities in adult SE patients were measured by the *Charlson Comorbidity Index* (CCI); high CCI increased the risk of death by 6.79 times in SE patients.[10] In children with solid mass tumors, the *Pediatric Comorbidity Index* (PCI) has been commonly used. A PCI ≥ 6 or CCI score of 3 was associated with increased mortality. The study also explains that the probability of survival in PCI is better than the degree of comorbidity in CCI.[6] A study used *Comorbidity Index* which was based on a study on the pediatric population with solid mass tumors,[6] while other study used *Charlson Comorbidity Index* in adult population with SE,[10] so further study is needed to evaluate which comorbidity index can be used in the pediatric patient population with SE.

In a previous study, etiological classification of SE was divided into acute (40.9%), remote (29.5%),

and idiopathic (29.5%), but such classification did not correlate with poor outcomes.[5] In contrast, we categorized etiology into infectious *vs.* non-infectious, as potential etiologies of acute symptoms. A previous study showed that more pediatric patients with SE who had an infectious etiology experienced poor functional outcomes, although the difference was not statistically significant.[2]

Mortality rate due to SE was 4-6% in children, lower than the adult mortality rate of 10-30%.[3] A study reported that the mortality rate due to SE in children was 3-11%, with the cause of death occurring either due to the underlying cause or to complications of SE itself.[11] In our study, the mortality rate in pediatric patients who were treated at Dr. Sardjito Hospital, Yogyakarya, Central Java, was 18.2%, higher than in previous studies. This observation was likely influenced by many factors, such as etiology or pre-existing patient comorbidities. Multivariate analysis of mortality outcomes revealed that PCI score, which measures the comorbidity of SE patients, indicating high comorbidities (PCI score ≥ 6) was associated with more deaths than SE patients with low comorbidities (PCI score <6) (P=0.008). The OR value of 5.53 indicated that SE patients with high comorbidities had a 5.53 times increased risk of death compared to those with low comorbidities (95%CI 1.55 to 19.65). The STEPSS and etiology of SE were not significantly different (P>0.05) between mortality groups.

Medical comorbidities improve the predictive accuracy of SE outcomes (mortality and morbidity), and reinforce that age and etiology are strong prognosticators in SE outcomes. Patients with higher comorbidities have worse outcomes.[12] Mortality is influenced by many factors, but death in SE patients is often caused by comorbidities or underlying disease, not as a direct result of SE.[13]

Infants <1 year of age have immature brains and body temperature regulation, so they are more susceptible to risk of persistent seizures.[6] As such, SE incidence is higher in children of younger ages.[12] Another source suggested that the fastest brain growth occurs in the first 2 years, with stimulated neurons forming new branches or synapses, and unstimulated neurons dying. Children aged <2 years have good neuroplasticity, so the brain has the ability to remodel and reorganize functions to adapt to new conditions.[14] This paradox means that although the very young are more susceptible to SE events, they can potentially better survive SE attacks and better adapt to new conditions, i.e., brain damage, because they have good neuronal plasticity.[14]

Generalized tonic-clonic seizures are associated with increased autonomic activity, up to a failure of cerebral autoregulation.[15] The GTC seizures involve lesions in both hemispheres, while partial seizures involve focal/unilateral lesions. Hence, the area of the lesion is more extensive in GTC seizures. The convulsive SE type tends to have poorer outcomes in post-SE developmental disorders.[16] Convulsive SE patients in a coma have higher mortality compared to non-convulsive SE patients with higher level of consciousness or somnolence.[17]

Patients who had a history of seizures before an SE episode had better outcomes than those without a previous history of seizures, because the former have plastic changes induced in neurons due to repeated seizures, thus increasing resistance to damage due to stimulation by SE.[5] Neuronal plasticity is the ability of the nervous system to adopt new functional and structural states. Chronic and acute disorders of the nervous system lead to reorganization of the neural cell circuits using plasticity mechanisms. The repair or remodeling process works more completely in children with nerve damage than in adults. Seizures or injury to the nervous system can cause reorganization of neural circuits that act like plasticity. Thus, a history of seizures can reshape connectivity at the functional and structural levels through the remodeling process.[18]

The mechanism of plasticity in epilepsy patients who experience recurrent seizures was demonstrated in an animal model. Rodents with repeated seizures underwent resectioning of the hippocampus, which is the focus of the epilepsy lesion (the area most prone to seizures). Further examination of the hippocampus area revealed synaptic fibers (plasticity) at the focus of the lesion. Seizures comprising of neural activity induce gene expression. In the dentate gyrus, seizures induce granule cell gene expression, as well as changes in other cell types. Under normal conditions, granule cells express several neurotropins, but in seizure conditions changes are influenced by the type and duration of the seizure. Other than seizures, ischemia and trauma are causes of neurotropic changes in granule cells. After a seizure, changes in potential neuromodulators occur, GABA expression increases,

and glutamic acid decarboxylase (an enzyme that synthesizes GABA) also increases. Seizures induce the dentate gyrus, as well as cause granule cells to express neurotropins and increase synaptogenesis. One of the released neurotropins is brain-derived neurotrophic factor (BDNF). The BDNF is a protein abundant in the brain and peripheral nerves that affects neurodevelopment, growth, and survival. This BDNF facilitates growth, development, and synaptogenesis, and can also protect cells from damage due to seizures by potentiating synaptic transmission pathways. In addition, BDNF induces neuropeptide Y (NPY), which has anticonvulsant effects and modulates the development and survival of newly formed granule cells after seizures (neurogenesis).[19]

A limitation of this study was the retrospective study design, as there may have been bias in data collection. Also, hospital-based studies and observations of short-term outcomes at the time of hospital discharge are limitations of the study, because long-term outcomes were not noted. Another limitation was that assessment of consciousness level (STEPSS component) was assessed when the patient is in SE and prior to receiving SE management. Because Dr. Sardjito Hospital is a tertiary referral hospital, some SE patients were referral cases who experienced SE in the previous hospital and previously received therapy. However, in such cases, we took the level of consciousness from medical records that included a history of the patient's condition before being referred.

In conclusion, we use the STEPSS to predict the outcomes of pediatric patients with SE. The STEPSS can be used as a predictor of functional outcomes of SE patients by assessing changes in POPC score, but not statistically significant in predicting mortality outcome. Further study needs to be done in multiple centers with larger sample sizes to confirm the predictive validity of STEPSS.

Conflict of interest

None declared.

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