

A study of critically ill children presenting with seizures regardless of seizure duration admitted in the PICU of a tertiary hospital in India

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ABSTRACT

Our aim was to study the clinical profile, immediate outcome and risk factors associated with poor outcome in critically ill children presenting with seizures requiring PICU admission. As seizures lasting 10 min or more can potentially cause brain damage, we included all children regardless of seizure duration. The records of 157 children aged 1 month to 16 years admitted in the PICU at a tertiary hospital in India with seizures as the presenting symptom during a three-year period were studied retrospectively. Median age of patients was 4 years. 34 (21%) had pre-existing epilepsy and 33 (21%) had previous developmental delay/neuro-deficit. Seizure duration was > 30 min in 75 (47.7%) and 56 (35.6%) required the use of more than 2 antiseizure drugs. 101 (64%) had acute symptomatic seizures, 28 (17%) remote symptomatic and 27 (17.1%) had unknown cause. New onset neurological deficit was seen in 18 (15.6%) and 14 (8.9%) died. Young age, high PEWS score at presentation, prolonged/recurrent seizures, CNS infection, need for multiple antiseizure drugs and ventilation/pressor use were risk factors for poor outcome. Neurological outcome and survival of children in our study were good. Further all-inclusive studies irrespective of seizure duration are needed to obtain a complete picture of critical children presenting with seizures.

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1. Introduction

The burden of acute neurologic affliction in pediatric population is high and contributes to 16.2% of the total admissions to pediatric intensive care units (PICU) globally [1]. Status epilepticus (SE) is the commonest neuro-emergency in children and as per epidemiological studies in western countries, it's estimated incidence in children (18–20 per 100,000 children per year) is much greater than the adult incidence of around 4–6 per 100,000 per year [2–5]. Despite advances in management, SE in children is associated with significant mortality as well as permanent morbidity in the form of epilepsy or neurological disability in developing countries like India.

The common causes of SE in children vary from region to region as evidenced by the differences in the results of studies conducted in developing and developed nations. Also, there are substantial differences between older and younger children in terms of etiology as well as outcome. For planning of management strategies and appropriate resource allocation, there is thus a need for regional demographic statistics.

Insight into risk factors associated with poor outcome is imperative for counseling of parents while the child is under intensive care. Population and hospital-based Indian studies required for this purpose are however limited.

Irrespective of the duration of seizure, children admitted to the PICU following seizures reflect severe end of the spectrum of disease. However, ICU based studies so far have limited themselves to including children with seizures lasting for more than 30 min, which has been the definition of status epilepticus until recently. Literature on critical patients presenting with seizures but who do not fit the definition of status is lacking owing to their exclusion. It is becoming increasingly recognized that seizure duration of 10 min or more can potentially lead to brain damage [6]. Studies show that longer the duration of convulsion before intervention, more is the difficulty in controlling it and more is the risk of permanent neurological damage [7]. In consideration of this, the International League Against Epilepsy (ILAE) while defining status epilepticus has proposed 5 min as the duration of seizure beyond which the seizure should be regarded as “continuous seizure activity” [8].

Thus, our aim in this study was to retrospectively evaluate all the children who presented with seizures at our hospital and required admission to the PICU in terms of their clinical profile & immediate outcome and to determine the risk factors for poor outcome.

Abbreviations: SE, status epilepticus; PEWS, Pediatric Early Warning Signs; ILAE, International League Against Epilepsy; ER, emergency room.

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2. Materials & methods

2.1. Study population

The study was conducted at MGM Hospital and Medical College, Maharashtra, India, which is an academic institution providing tertiary care under both public and private sector. It is situated at the junction of the Mumbai-Pune Expressway and four other major roadways connecting rural areas of Raigad District to the city. It caters to the urban population in its vicinity and owing to its location, is also the nearest tertiary hospital of referral for the primary health centers and rural sub-district hospitals in Raigad District. Patients with drug resistant seizures are referred to our hospital for intensive care & advanced diagnostic workup, thus providing us with a combination of urban as well as rural patients.

2.2. Treatment protocol

The protocol for management of active convulsion followed at our hospital is based on consensus guidelines provided by Association of Child Neurology, Indian Council of Medical Research [9] and includes intravenous midazolam boluses as the first line antiseizure drug followed by loading of a second line drug. Fosphenytoin is the most commonly used 2nd line drug in our hospital. Ongoing therapy of the child with a broad-spectrum antiseizure drug belonging to a different class is one of the exceptions to its use. Seizure that persists despite the use of two doses of initial benzodiazepine and a second antiseizure drug is treated in the intensive care unit. Drug resistant seizures are treated with loading doses of levetiracetam and convulsions continuing despite third anticonvulsant are started on continuous midazolam drip. Patients who achieve seizure control with use of 2 antiseizure drugs or less but are treated in PICU include those falling under high risk category according to PEWS score and presence of new onset focal neurologic deficit or traumatic brain injury.

2.3. Study design and inclusion criteria

We did a retrospective study of medical records of children in the age group 1 month to 16 years who presented with seizures at our institute and required admission to intensive care unit. Approval of Institutional Ethics Committee was obtained. In contrast to other studies, duration of seizure activity was not the inclusion criteria in our study. Children who were admitted to PICU for non-neurological emergencies and later experienced seizures during their course in the hospital were not included. Records of 157 children admitted in a three-year period (March 2015–February 2018) were analyzed. Details regarding clinical presentation, past medical history, Pediatric Early Warning Signs score (PEWS) at presentation, lab/imaging reports, treatment received, etiological diagnosis, and immediate neurological outcome were noted.

2.4. Definitions

Seizures were classified based on ILAE report on definition and classification of status epilepticus, 2015 [8]. Poor outcome was defined as death during course in PICU or presence of persistent new onset neurological deficit at discharge from hospital. Neurological deficit was defined as a score of less than 15 on the pediatric Glasgow Coma Scale (GCS) or presence of focal deficits on neurological examination. Development of cognitive deficit during course in hospital was not assessed.

2.5. Statistical analysis

Descriptive statistics were summarized as percentages. Categorical variables were tested for association using the Pearson's chi-square test and Fisher's exact test wherever appropriate. A p level of <0.05 was considered statistically significant.

3. Results

Out of 1421 children admitted to the PICU at our hospital over a three-year period, 157 (11%) were admitted after presentation to the emergency room with seizures.

3.1. Patient characteristics

Patient characteristics are summarized in Table 1. Majority of children in our study were under 5 years old with a median age of 4 years. The number of males and females was comparable. Most children (79%) had no prior history of seizures and were previously developmentally and neurologically normal. At presentation in the emergency room, 92.9% children were identified to have high risk for rapid clinical deterioration based on calculation of the PEWS score.

3.2. Seizure characteristics

As shown in Table 1, generalized tonic-clonic seizures were more frequent than focal seizures. Half of the children (52.2%) had seizures lasting for less than 30 min but required PICU care. 50 (31.8%) patients had recurrent seizures during their stay in PICU despite initial control of seizures with antiseizure drugs.

3.3. Treatment received

Intravenous midazolam followed by fosphenytoin were the most commonly used drugs. 56 (35.6%) patients required the use of more than 2 types of antiseizure drug and 27 (17.1%) required 4 or more types of antiseizure drug for control of seizures. Midazolam infusion was given in 26 patients and 1 patient received thiopentone. 31 (19.7%) patients required ventilatory support and 24 (15.2%) required pressor support.

3.4. Etiology

Fig. 1 illustrates the etiology of seizures. 101 (64%) patients had acute symptomatic seizures, 28 (17%) had remote symptomatic

Table 1
Patient & seizure characteristics (n = 157).

	Number (%)
Patients admitted to the PICU with seizures	157
Age	
Less than 2 years	58 (36.9)
2–5 years	56 (35.6)
6–16 years	43 (27.3)
Median age (years)	4
Gender	
Male	77
Female	80
History of pre-existing epilepsy	34 (21)
History of developmental delay/neuro deficit	33 (21)
PEWS score	
Score 3/3 in category 'behavior'	101 (64.3)
Total score \geq 5/9	88 (56)
High risk	146 (92.9)
Type of seizure	
Generalized tonic-clonic	104 (66.2)
Focal	39 (24.8)
Unknown	14 (8.9)
Seizure duration	
Less than 30 min	82 (52.2)
More than 30 min	75 (47.7)
30–60 min	30
60 min–24 h	38
More than 24 h	7
Recurrent seizures	50 (31.8)

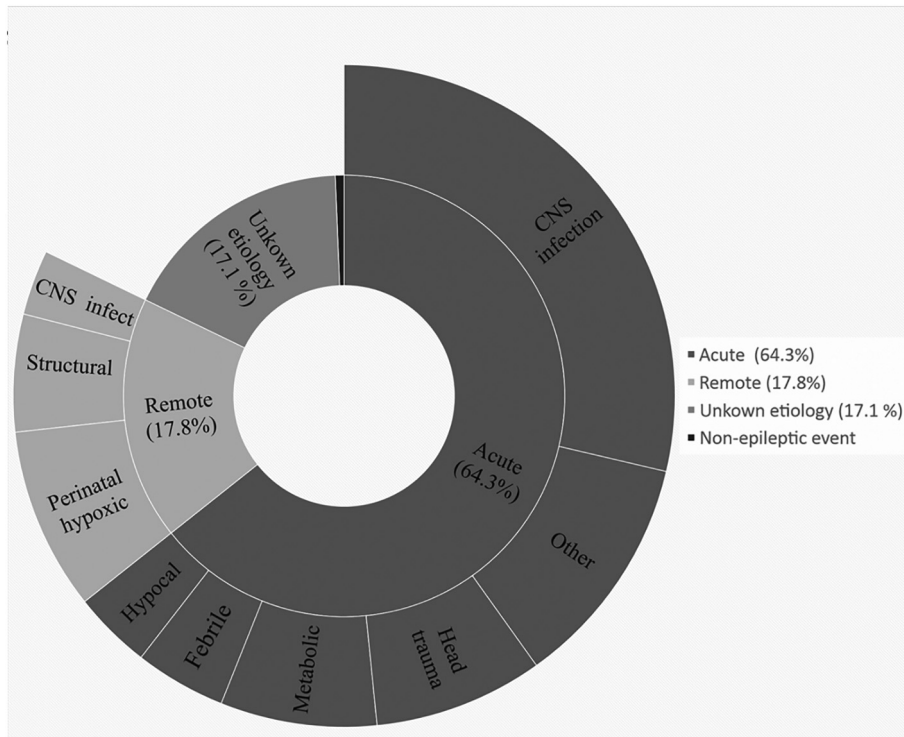


Fig. 1. Etiology (n = 157).

seizures, cause could not be identified in 27 (17.1%) patients and 1 had non epileptic event. 45 patients had CNS infections which constituted 28.6% of the PICU admissions following seizures (viral meningoencephalitis (26), tubercular meningitis (10), pyogenic meningitis (4), cerebral malaria (2), rickettsial meningoencephalitis (1), neurocysticercosis (1) and toxoplasmosis (1)). Other causes of acute symptomatic seizures included traumatic brain injury (13), metabolic disorders such as organic acidemias, aminoacidopathies, mitochondrial diseases, lipid storage disorders and other inborn errors of metabolism (12), prolonged febrile seizures (7), hypocalcemic seizures (6), hypertensive encephalopathy (4), hypoxic seizures (4), epileptic encephalopathy (3), VP shunt block (3), hypoglycemic seizures (2) and stroke (2). Causes of remote symptomatic seizures were perinatal insult (14), structural abnormality (9) and CNS infection in the past (5). 5 children presented with new onset refractory status epilepticus (NORSE) out of which 3 had history of fever prior to and during presentation. However, these patients were classified under unknown etiology as further evaluation of these cases remained incomplete and autoantibody testing was not done.

The etiology of seizures across age groups is illustrated in Fig. 2. No significant correlation was seen between age of the child and etiology of seizure ($p = 0.63$).

3.5. Diagnostic workup

EEG was performed during hospital stay in 59 (37.5%) patients and 28 (47.4%) patients had abnormal recordings. EEG abnormalities included focal waveform abnormalities (7), multifocal waveform abnormalities (4), diffusely slow background activity (7), periodic discharges (6) and low voltage recording (4). Data on EEG performed on patients at follow up after their discharge from hospital was not available. Neuroimaging was performed in 122 patients, out of which 74 (60.6%) showed abnormality. MRI was done in 112, CT in 21 patients and 11 patients underwent CT followed by MRI. Imaging findings include meningitis/meningoencephalitis (22), hypoxic injury (14), hydrocephalus (9), intracranial bleed (7), space occupying lesion (5), cerebral atrophy (5), cortical dysplasia (4), posterior reversible encephalopathy

syndrome (2), mesial temporal sclerosis (2), venous thrombosis (2) and diffuse cerebral edema (2).

3.6. Characteristics of children with pre-existing epilepsy

Out of 34 (21%) patients with pre-existing epilepsy, 23 had generalized and 11 had focal epilepsy. Majority of the patients (25) had symptomatic epilepsy. Etiologies were perinatal hypoxia/neonatal hypoglycemia (9), CNS infection including post tubercular communicating hydrocephalus (10), cortical dysplasia (3) and metabolic encephalopathy (3). 9 patients had unknown etiology (generalized epilepsy (7), focal epilepsy (2)). 3 had epileptic encephalopathy and 4 patients with generalized epilepsy could not be classified due to unavailability of EEG report. 3 patients had Lennox–Gastaut syndrome and 5 had temporal lobe epilepsy. Neuroimaging was normal in 7, showed abnormality in 21 and was not performed in 6 patients. EEG was normal in 9, showed abnormality in 14, and was not done in 11 patients.

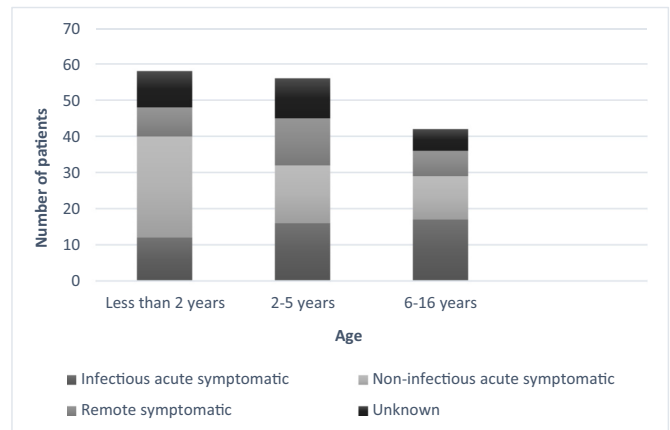


Fig. 2. Etiology of seizures according to age.

18 patients were on monotherapy prior to presentation. 9 patients were receiving two antiseizure drugs, 5 were receiving three to four antiseizure drugs and 3 patients were not on any antiseizure drug. Non-compliance to therapy was the reason for occurrence of seizures in 2 patients while 12 had intercurrent illness. Seizures occurred during antiseizure drug therapy tapering in 5 patients and 1 patient had acute ventriculoperitoneal shunt block.

3.7. Mortality

14 of the 157 patients (8.9%) admitted with seizures died during stay in PICU as compared to an average all-cause mortality rate of 12.1% in our PICU. Out of the patients who died, 6 had remote symptomatic epilepsy with breakthrough seizures, 4 had viral encephalitis, 2 had metabolic encephalopathy, 1 had hypoxic seizures and cause was not known in 1 patient. Cause of death in these patients was septicemia (4), respiratory failure following pneumonia (3), intractable seizures (3), brain herniation (2), and severe acidosis (2). Infection (sepsis/pneumonia) was the cause of death in majority of patients with remote symptomatic epilepsy. Factors significantly associated with mortality are shown in Table 2.

3.8. Neurological outcome

Out of 115 children who survived and had no previous developmental or neurological abnormality, 18 patients (15.6%) developed new neurological deficit. CNS infection was the cause in 13 out of 18 patients (72.2%). Causes include tubercular meningitis (8), metabolic encephalopathy (5), viral meningoencephalitis (3), pyogenic meningitis (1) and rickettsial encephalitis (1). 28.8% (13 out of 45) of patients with CNS infections and 80% (8 out of 10) of patients admitted with tubercular meningitis developed neurological deficit. Statistically significant risk factors for development of new neuro-deficit are shown in Table 2.

3.9. Risk factors for poor outcome

Factors showing significant association with poor outcome, that is either death or development of new neurological deficit, are shown in Table 3. The presence of CNS infection as the underlying etiology of seizure was a significant risk factor for poor outcome. Among individual etiologies, tubercular meningitis and metabolic encephalopathy were also significant predictors of poor outcome (p < 0.001). Other important factors predicting poor outcome were age less than 2 years, seizure

Table 3
Risk factors predicting poor outcome.

Risk factor	Poor outcome (death or new neurological deficit)	Favorable outcome	p value
Age			<0.001
<2 years	20	38	
≥2 years	12	87	
Seizure duration			<0.05
<30 min	21	54	
≥30 min	11	71	
Recurrent seizures			<0.001
Yes	24	26	
No	8	99	
High risk on PEWS score			<0.001
Yes	31	115	
No	1	10	
No. of drugs			<0.001
≤2	18	38	
>2	14	87	
CNS infection			<0.001
Yes	17	28	
No	15	97	
Ventilatory support			<0.001
Yes	20	11	
No	12	114	
Pressor support			<0.001
Yes	20	4	
No	12	121	

duration of more than 30 min, presence of recurrent seizures, PEWS score falling in the high risk category, need to use more than 2 antiseizure drugs and need for ventilatory/pressor support.

3.10. Characteristics of children with recurrent seizures

7 patients had a delay in presentation to the hospital and suffered from prolonged as well as recurrent seizures without regaining consciousness for more than 24 h. Out of these, 3 patients had pre-existing epilepsy with breakthrough seizures, 3 had CNS infection and 1 had metabolic disorder. All 7 patients had drug resistant seizures with need for midazolam infusion to control seizures in 4 patients. Ventilatory support was required in 4 and 2 required pressor support. 5/7 had poor outcome (death in 3 and new onset neurodeficit in 2).

50 children had recurrent seizures after initial achievement of seizure control in the hospital. Since it was identified as a risk factor for

Table 2
Risk factors for new onset neurological deficit and immediate mortality in children admitted in PICU with seizures (statistically significant results denoted by *).

Risk factors	New onset neurological deficit			Mortality			
	Developed neurological deficit	No deficit	P value	Died	Survived	P value	
Age	<2 years	13	31	<0.001*	7	51	0.288
	≥2 years	5	66		7	92	
Seizure duration	<30 min	6	57	0.046*	5	77	0.194
	≥30 min	12	40		9	66	
Recurrent seizures	Yes	15	16	<0.001*	9	41	<0.006*
	No	3	81		5	102	
PEWS score	<3 in category behavior	1	33	0.001*	1	55	<0.019*
	=3 in category	17	64		13	88	
	<5 total score	8	32	0.38	1	68	0.003*
	≥5 total score	10	65		13	75	
No. of drugs required	≤2	8	91	<0.001*	4	118	<0.001*
	>2	10	6		8	27	
Etiology	CNS infection	13	30	<0.001*	4	41	
	Remote symptomatic	-	-		6	22	0.010*
	Other	5	67		8	121	
Ventilatory support	Yes	7	7	<0.001*	13	18	<0.001*
	No	11	90		1	125	
Pressor support	Yes	6	2	<0.001*	14	10	<0.001*
	No	12	95		0	133	

poor outcome, we further studied the characteristics of these children. 27 children less than 2 years, 14 between 2 and 5 years and 9 between 6 and 16 years had recurrent seizures. Thus, their occurrence was significantly more in younger children ($p < 0.01$). 35/50 children had 1st episode of seizure at presentation while 15/50 had pre-existing epilepsy. 30/50 had at least one seizure lasting for more than 30 min. 39 patients required use of more than 2 antiseizure drugs, 17 required ventilatory support and 12 required pressor support. 40/50 patients had acute symptomatic etiology.

4. Discussion

To our best knowledge, this is a first of its kind study evaluating critically ill children who presented with seizures and required management in intensive care unit, irrespective of the duration of the seizure. Due to lack of studies with similar study design, we compared our results to studies including children with status epilepticus (continuous seizure activity lasting for 30 min or longer, or intermittent seizure activity lasting for more than 30 min without regain of consciousness) admitted to the PICU. Half of the children (52.2%) in our study had seizures lasting for more than 5 min but less than 30 min. This throws light on the large number of critical children who may have been left out of the definition of SE in previous studies.

In our study, the median age was 4 years. Studies conducted in developing as well as developed countries have shown similar results having younger age at presentation [10,11,12]. This may be attributable to the low threshold for seizures in young children and their vulnerability to acquired disorders involving the CNS. A study conducted by Shinnar et al. [10] found a strong effect of age on cause of status epilepticus, where febrile and other acute symptomatic etiologies were more common in less than 2 years of age and unknown & remote symptomatic etiologies were more common in the older children. However, this correlation was not seen in our study and there was no significant difference in the occurrence of acute or remote symptomatic seizures across age groups (Fig. 2, $p = 0.636$). Our findings show that age less than 2 years is a significant risk factor for poor immediate neurological outcome (Table 2, $p < 0.001$). Similar findings have been seen in a study by Sadarangani et al. [13]. This highlights the criticality of managing these patients promptly and appropriately in order to ensure neurologically intact survival.

The Pediatric Early Warning Signs (PEWS) score of all the patients presenting to the ER at our hospital is calculated for identification of patients at risk for rapid clinical deterioration and need of higher level of care. It is based on objective assessment parameters to determine the overall status of the patient and looks at three categories: behavior (neurological), cardiovascular and respiratory, with scores ranging from 0 to 3 in each category and a maximum total score of 9. A PEWS score of 3 in any one category or a total score of 5 or more has a very high risk [14]. In our study, a significant association was seen between PEWS score and outcome.

21% patients in our study had pre-existing epilepsy as compared to 69.7% in a 5-year retrospective study conducted in PICU in USA [15], 36% in a similar study conducted in UK [11], 46.6% in study conducted in Delhi, India [12] and 25.7% in a study in Bihar, India [16]. It is noteworthy that almost 80% of our patients presented with 1st episode of seizure due to the differences in underlying cause and approach to management posed by it. Generalized tonic-clonic seizures were the most common type seen in our study and type of seizure did not have any association with underlying etiology or outcome. Patients with seizures lasting less than 30 min had low morbidity and good immediate neurological outcome despite being critical. Further studies to determine long term neurological morbidity in these patients are however needed in the Indian setting. 38 patients had seizures lasting for 60 mins to 24 h and 7 patients for more than 24 h. This is because patients from remote rural areas are referred to our hospital for management of SE and at times, poor transportation facilities lead to a delay in initiation of

treatment. Seizure characteristics such as duration, number of drugs needed to achieve control and presence of recurrent seizures had an association with outcome as seen in multiple studies [12,16,17].

64% children had acute symptomatic seizures and CNS infections constituted a majority of these. Cause could not be identified in 17.1% children and includes the children in whom investigations necessarily for diagnosis could not be performed. There are differences in underlying etiology between developed and developing countries owing to better healthcare facilities. In a study in UK by Hussain et al. [11], 34% had prolonged febrile seizure, 28% had remote symptomatic, 11% had acute exacerbation of a pre-existing idiopathic epilepsy and only 18% had acute symptomatic seizures. A systematic review [18] reported that 1% to 12% of children from countries in the developed world presenting with SE have infectious cause as compared to 28.6% seen in our study. An 8-year review of PICU admissions in a hospital in South Africa [17] showed an infective cause in 43% cases, whereas an Indian study conducted in Bihar [16] showed 38.5% cases. Thus, infections are still a major cause of pediatric SE in developing countries like India and the scope of preventive strategies in reducing its burden is large. In our study, 30% of the CNS infections were caused by vaccine preventable diseases.

A systematic review of the outcome of convulsive status epilepticus in children showed that most studies report neurological sequelae in less than 15% and that cause is the main determinant of outcome [19]. The poorest outcome is reported in acute symptomatic status patients with neurological dysfunction in more than 20% of cases. Our results are consistent with this finding as all children who developed neurodeficit in our study had acute symptomatic seizures with CNS infection being the underlying etiology in 70% and metabolic encephalopathy in remaining 30%. A systematic review of 63 studies conducted worldwide showed that mortality among children admitted to PICU with status epilepticus is 5–8% [19]. Indian studies have reported higher rates of 16.7% from Kashmir [20], 30% from Delhi [12] and 31.4% from Bihar [16]. This contrasts with our study which had a mortality rate of 8.9%. Delay in initiation of treatment, differences in access to health care facilities between urban and rural areas of India and variable management protocols across centers may be the reason for vast differences in mortality rates seen in Indian studies.

We found a number of risk factors which had significant association with poor outcome. Although a causative effect cannot be established from our study, the recognition of factors predicting poor outcome will help in early risk stratification for aggressive management. Mortality associated with pediatric status epilepticus in India is on the fall. There is now a need to shift focus on neurologically intact survival. An alternative approach to management which focuses on neuroprotective measures based on risk stratification for adverse neurological outcome could be the solution in resource poor settings.

4.1. Limitations

The evaluation of neurological outcome in our study was retrospective and was based on documentation of GCS score and deficits detected on physical examination. The presence of cognitive or behavioral deficits may have been overlooked in the absence of formal methods of assessment.

5. Conclusion

A large number of critical children may have been left out in previous studies due to the use of 30-min seizure duration as the criteria for SE. Further all-inclusive studies such as ours are needed to obtain a complete picture. In our study, neurological outcome and survival of children following admission to PICU with seizures were good. Risk factors significantly associated with poor outcome were age less than 2 years, a high risk PEWS score at presentation, prolonged seizures,

recurrent seizures, CNS infection as the etiology, need for multiple anti-seizure drugs and need for ventilatory/pressor support. CNS infections were a major underlying cause in children admitted to PICU with seizures in our study and this emphasizes the scope of preventive strategies in reducing disease burden in developing countries like India.

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Ethical statement

Approval of institutional ethical committee was obtained prior to conducting the study. The study was conducted in accordance with their recommendations.

Declaration of competing interest

The authors declare no potential conflicts of interest.

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