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SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA



PREDICTION MODEL FOR OUTCOME OF PATIENTS WITH SUPER REFRACTORY STATUS EPILEPTICUS- A multicentre study

Thesis submitted in partial fulfilment of the rules and regulations

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Sree Chitra Tirunal Institute for Medical Sciences and
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By

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PDF in Electroencephalography

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DECLARATION

I, Dr. Jithu Jose, hereby declare that this project titled '**PREDICTION MODEL FOR OUTCOME OF PATIENTS WITH SUPER REFRACTORY STATUS EPILEPTICUS- A multicentre study**' was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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The candidate, Dr. Jithu Jose, has completed the project titled 'Electro-Clinical and Radiological predictors of outcome In Super Refractory Status Epilepticus' under my guidance.



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Dr. Jithu Jose

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1. SYNOPSIS

Purpose – We conducted this study to determine clinical electrophysiological predictors of outcome in Super Refractory Status Epilepticus (SRSE)

Methods – Data's were collected retrospectively from case records who were admitted with the diagnosis of SRSE from 2011 to 2021 from SCTIMST (Data controller) and 9 other centres (Data providers) fulfilling data sharing agreement norms .Functional outcome was measured by Glasgow outcome score (GOS) and dichotomised to a bad outcome (< 2) and good outcome (> 3).

Results – 200 SRSE patients were identified during this Multicentre study .Acute Symptomatic (88- 44%) was the most common etiology. Focal onset generalised Seizures was the common seizure type 116 (58%) and 116 (58%) were diagnosed to have New Onset Refractory Status Epilepticus and 71 patients were under FIRES subtype. 80 (40 %) patients had a bad outcome. Univariate analysis showed duration of ICU stay (P- .0017), acute symptomatic etiology (p-0.043), After Status Epilepticus Discharges (p - .030) , delay in starting anaesthetics (p<.001) , need for vasopressors (p-.001) , number of ASM (p-.004) and immunotherapy delay (p- <.001) as independent predictors of outcome .Multivariate analysis showed acute symptomatic etiology (P-0.024)and delay in starting anaesthetics (P- < .001) as predictors of bad outcome .Burst suppression with anesthetics (P- 0.036) and need for vasopressors (P-0.004) was associated with good outcome.

Conclusions – We could determine independent therapeutic and electrophysiological prognostic factors and a uniform protocol driven approach is needed for the effective management of this entity

Key words – SRSE- Super Refractory Status Epilepticus ASM – Anti Seizure Medication FIRES –Febrile Infection Related Epilepsy Syndrome, NORSE – New Onset Refractory Status Epilepticus

2. INTRODUCTION

Super refractory status epilepticus (SRSE) is an important neurological emergency. It is defined as status epilepticus that continues for more than 24 hours despite the use of anaesthetic therapy. It was a term first used in third London Innsbruck colloquium on status epilepsy held at oxford in July 2011 (1). In many studies it is found that this condition is associated with significant mortality (40 % to 54%) and morbidity [see; Annexure 4]. Majority of the times SRSE occurs de nova in a healthy brain without any prior history of illness (2).

We conducted a retrospective study from our own institute regarding the predictors of outcome in SRSE and were able to identify the predictors of outcome and has been published. The prognosis in SRSE was not dismal as thought of and a good planned protocol is required for the management of SRSE (3). However there are no multicentre trial and Randomised controlled trial so far available with SRSE. In this study we want to study the predictors of outcome in SRSE recruiting much larger number of patients from multiple centres for our study.

3. REVIEW OF LITERATURE

Super refractory status epilepticus (SRSE) is defined as continuous or recurrent seizures without normalization of consciousness lasting for 24 h or more despite administration of an intravenous (IV) anesthetic (midazolam, propofol, ketamine, or barbiturate), or recurrence of status epilepticus (SE) on weaning of IV anesthetics (1). In a prospective study, 9% (12/128) of SE episodes failed second-line antiepileptic drugs (AEDs) and required coma induction. The term SRSE was introduced in 2011 in London-Innsbruck Colloquium; therefore, there is paucity of information on SRSE (1).

SRSE is more likely following acute brain injury rather than chronic epilepsy and is more likely after central nervous system (CNS) infection, stroke, or in a healthy brain with new onset refractory status epilepticus (3). The predictors of refractory status epilepticus (RSE) are acute SE etiology, coma/stupor, and serum albumin <3.5 g/l (4). Development of RSE or SRSE was associated with stupor or coma on admission and absence of history of epilepsy. These patients had a worse outcome compared to those who responded to AEDs (5). Infections can also complicate SE and are associated with a poor outcome (6). The etiology of SRSE in the developing countries is dominated by CNS infections (7). SRSE can be convulsive or non-convulsive. The convulsive SE can result in serious complications such as myocardial injury, aspiration pneumonia, pulmonary edema, and rhabdomyolysis leading to renal failure. The diagnosis of non-

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convulsive SE (NCSE) requires electroencephalography (EEG), which may delay the diagnosis. SE may occur due to failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms leading to prolonged seizures (t1).

Persistence of SE can cause long-term sequelae (after time point t2) including neuronal injury, neuronal death, and alteration of neuronal network depending on the type and duration of seizures. For convulsive SE, t1 is 5 min and t2 is 30 min. For other types of seizures, t1 and t2 are not known (8). There is paucity of studies on SRSE, and the available information is based on retrospective review of cases. From China, 13 patients with SRSE were reported during January 2010 to August 2013 (9); from France, 78 patients were collected in an intensive care unit (ICU) survey during 2001 to 2011 having SE more than 7 days of anesthesia (10), and from South India (Hyderabad) 30 (16.9%) patients, and from Vellore 17 (7.7%) events of SRSE were reported (11, 12). In a recent population-based survey from Germany, during 2008 to 2013, 338 out of 2,585 (13%) patients with SE had SRSE (13). Status epilepticus is broadly defined as a seizure activity that continues for 30 min or recurrent seizures without recovery between attacks. Experimental evidence suggest that irreversible neuronal injury may start after 20 to 30 min of generalised convulsive status epilepsy (fujikawa 1996; Meldrum and Brierley, 1973). So every effort has to be made to stop seizure activity prior to that.

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Super refractory status epilepticus is associated with high mortality of 45-50 %. Data about clinical and MRI predictors of outcomes in this category are very scarce, although refractory status epilepsy has been studied extensively. In kantanen et al, 3 years Finland retrospective study incidence of super refractory status epilepticus was found to be 5 to 10% of all status epilepsy(.7 per 100000) . Yaohua Li et al study of SRSE Patients in West China Hospital, Sichuan University, between January 2010 and August 2013, were retrospectively analysed. Outcome at discharge, at the three-month and long-term follow-ups were evaluated using the Glasgow Outcome Scale (GOS). Possible predictors of mortality and outcome were also evaluated. Thirteen patients with SRSE were included. Young patients with encephalitis accounted for the majority of the series (61.5%). In-hospital mortality was 15.4% (2/13), and the three-month mortality was 36.4% (4/11; two patients ceasing therapy were excluded). At the long-term follow-up, 18.2% of patients improved and 45.5% of patients recovered. Patients of older age and those with multiple complications had higher mortality compared with those of younger age and those with fewer complications. For survivors, functional outcome had significantly improved at three-month follow-up (GOS score = 4.1 1.2) compared to that at discharge (GOS score = 3.1 1.2, $P < 0.05$). Long duration of anaesthesia, aetiology of encephalitis and positive neuroimaging findings tended to be associated with poor functional outcome.

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How seizure become refractory :

Seizures are sustained by either imbalance of neuronal excitation and inhibition or failure of normal inhibitory mechanisms [8]. γ -Aminobutyric acid (GABA) is the commonest inhibitory neurotransmitter, preventing neurons from excess excitation by activation of the GABAA receptor, and glutamate is the commonest excitatory neurotransmitter, and mediates excess excitation via the N-methyl- D-aspartate (NMDA) receptor. Second, SE can become self-sustaining, with neuronal damage and pharmacoresistance becoming apparent after 30 min of continuous seizure activity in both experimental and clinical studies [9–13]. As SE continues, there is a progressive development of pharmacoresistance to benzodiazepines [10], and NMDA receptor blockers such as ketamine can remain effective late in the course of SE [14]. This is likely explained by intensified “receptor trafficking,” in which the number of glutaminergic receptors at the cell surface increases and the number of GABA receptors decreases [15–17], leading to a reduction in GABAergic activity. There are likely many other mechanisms contributing to the development of RSE and SRSE, which include (1) mitochondrial failure or insufficiency[18], (2) inflammatory processes [19, 20] resulting in decreased integrity of the blood–

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brain barrier and higher potassium levels [21, 22], and (3) changes in gene expression [23].

Evaluation of patient with Refractory and super refractory seizures

CSF Analysis

. A lumbar puncture for CSF analysis must be performed in immunocompromised patients, patients with a history and/or examination findings suggestive of central nervous system infection, and any patient with an unidentified cause of SE. CSF should be sent for analysis of blood cell count, glucose concentration, protein concentration, Gram staining, and select bacterial and viral cultures as well as polymerase chain reaction studies depending on the age, comorbidities, and social history of the patient. If the initial CSF studies are not suggestive of infection and the cause has still not been identified, additional CSF analysis should be considered, including cytology and an autoimmune panel including anti-NMDA receptor antibodies and voltage-gated potassium channel antibodies. Other tests such as GAD-65 antibody and comprehensive paraneoplastic panels can be tested if there is concern about CNS involvement or limbic encephalitis respectively.

EEG as a tool in Refractory seizures

Continuous electroencephalography is generally initiated within 1 h of the onset of SE for detection of subtle clinical or subclinical electrographic seizures. In addition, there are early data suggesting that specific EEG patterns can be associated with specific causes such as the extreme delta brush seen in cases of anti-NMDA receptor encephalitis. Continuous EEG monitoring is required at this point as anesthesia should be titrated until there is cessation of all electrographic seizures and/or the burst-suppression pattern. However, the ability of electroencephalography to clearly differentiate between ictal and interictal patterns is not always straightforward in this setting. Periodic discharges are often present (either lateralized or generalized), and can demonstrate fluctuation or subtle evolution as well as superimposed fast or rhythmic activity, which can make the distinction between ongoing SE and the transition to the interictal or postictal state uncertain. Therefore, titration of the anesthetic agent to a burst-suppression pattern should be considered when faced with these particular EEG patterns that occur in between or subsequent to periods of definite electrographic SE. Continuous EEG monitoring has also revealed that seizures may still arise from a burst-suppression pattern, so careful ongoing monitoring is required [30]. However, when rare electrographic seizures continue to recur, it is uncertain if

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these isolated electrographic seizures result in significant additional neuronal injury. Therefore, the risks of escalating doses of anesthesia to attain an isoelectric or flat EEG background in order to suppress rare isolated seizures may not be justified. A burst-suppression pattern is typically maintained for 24 h before initiating a slow, controlled reduction in anesthesia with concurrent EEG monitoring to detect recurrent seizures.

MRI in SRSE

Brain imaging findings in affected patients have been reported in few case series and some case reports. This article is a comprehensive review of the magnetic resonance imaging (MRI) characteristics in all reported patients with a diagnosis of SRSE, describing the findings in the acute and chronic phases of the disease, and discussing possible pathogenesis and radiological differential diagnoses. Most of the patients had normal brain scans in the acute phase (61%) and about 25% of the patients reported in literature had abnormalities in the temporal lobes. Changes in the basal ganglia and rarely in thalami or brainstem have also been described, as well as diffuse cerebral edema in a minority of patients during the acute phase. The chronic phase of the disease was characterized by atrophic

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changes and evidence of mesiotemporal sclerosis. An understanding of these MRI abnormalities is necessary to support the diagnosis of SRSE and exclude mimics

4. OBJECTIVES:

Our study focuses on Super Refractory Status Epilepticus with an aim

1. To study the clinical, electrical and radiological profile of patients with SRSE
2. To develop a prediction model for outcome of patients with SRSE

These outcome models will help clinicians to formulate strategies to improve the outcomes in SRSE.

5. METHODS

200 Patients who were admitted in neurology services at SCTIMST (data Controller) and 9 other centres (data providers) during the study period (2011 to 2021) with the diagnosis of SRSE and satisfying the inclusion criteria were included.

These patients were recruited through a retrospective review of a prospectively maintained cohort of status epilepticus patients in each of the participating centres. Patients regardless of their age, sex, ethnic predilection will be recruited if they satisfy the definition of SRSE. However patients with psychogenic status epilepticus, Epilepsia Partialis Continua, SRSE controlled from outside the study centres and incomplete data will be excluded

5.1. DATA COLLECTION AND PROCEDURES

Data's were collected from case records who were admitted with the diagnosis of SRSE from 2011 to 2021 from SCTIMST (Data controller) and 9 other centres (Data providers) fulfilling data sharing agreement norms. Excel sheet containing all the variables to be filled for the collection of data will be sent to all the data providers. Data will be extracted from prospectively maintained SE registry which is stored as electronic medical records and is coded separately or from case records and case sheets where electronic records are not available. Demographic data, clinical profile, investigations, management strategies, complications during the stay, and follow-up data were gathered from the records and analyzed using a standard data collection Performa by the primary investigator and co investigators. The etiologies were categorized according to ILAE definitions (acute symptomatic, remote symptomatic, progressive symptomatic, or cryptogenic) and we calculated the Status Epilepticus Severity Score (STESS) for every episode at onset. A STESS score of 3 or more points was considered unfavorable and episodes were dichotomized accordingly. Continuous EEG data recorded from all SE patients will be retrieved from the compiled and stored EEG data.

5.2 OUTCOME DEFINITION

Functional outcome was measured by Glasgow outcome score (GOS) at the time of hospital discharge and also at the last available follow-up. GOS score <2(1,2) was considered poor outcome and > 3 (3,4,5) as good outcome for statistical analysis.

5.3 STATISTICS

Data were analysed with SPSS 21.0 software (SPSS Inc. Chicago). Descriptive analyses of numerical data were done with mean and standard deviation and categorical data with proportions. Predictors of outcome were analysed by univariate followed by multivariate analysis. Numerical data were analysed via T-test or Mann-Whitney U test and categorical data by Chi-square test and Fisher exact test. If p was < 0.1 then multivariate analysis using logistic regression was done. A two-tailed p -value of < 0.05 was considered statistically significant.

6. RESULTS

6.1 Study population

A total of 2196 Status Epilepticus patients were identified during the study period from January 2011 up to December 2021 from all the centres. Among those with Status Epilepticus 284 were excluded from further analysis due to inadequate data, error in coding lost to follow up, and missed case records, thereby leaving 1912 patients with SE for the final analysis of which 390 patients (20.3%) had satisfied the criteria of RSE and 200 (10.4 %) patients were SRSE.

6.2 Demographics and Clinical profile

The mean age of the patients in the study group was 34.145 ± 28.69 years, males were 58.5 %, while females were 41.5%. Thirty percent of patients had prior comorbidities (previous history of stroke, trauma, tumour, or seizures) among which prior history of seizures 43(23.5%) was the most common. SRSE was generalized or unknown in 84 (42 %) and focal onset in 116 (58%) patients.

Aetiologies of SRSE were taken retrospectively from the data registry and were classified according to ILAE definitions (acute symptomatic, remote symptomatic, progressive symptomatic, or cryptogenic). Acute symptomatic etiology 88 (44%) were the most common cause of SRSE followed by

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Cryptogenic 65 (32.5%), remote symptomatic 26(13%) and progressive symptomatic 21 (10.5%), shown in (Figure; 1). New-onset refractory status was seen in 116(58%) patients among which Febrile infection-related epilepsy syndrome (FIREs) was seen in 71 (35.5%)

Patients were managed in ICU in concordance with SE guidelines 2012) (3).Continuous intravenous anaesthetic agents were administered either combined or alone. The preferred first-line agent in use was Midazolam in 198 (99%) of patients followed by Ketamine 88 (44%), Propofol 37 (18.5%), isoflurane 18 (9%). Immunotherapy was given for 111(55.5%) suspecting autoimmune etiology and 28 (14%) patients among them had a confirmed diagnosis of AIE based on the consensus statement of the international encephalitis consortium 2012 , (IVIG with IVMP- 69 (34.5%) , IVMP alone - 110 (55%) , Rituximab 26 (13%) , PLEX 11 (5.5%) , Cyclophosphamide 11(5.5%) , AZT 2 (1%) , ACTH 11 (5.5%) patients).

Mean number of Anti-Seizure Medication in use was 5.71 ± 2.5 , and mean number of anaesthetics was 2.07 ± 0.98 . (36.5%) of patients achieved BSP with single anaesthetics and 53 (26.5%) achieved with two anaesthetics, 15 patients (9.2%) with 3 anaesthetics. Midazolam was the most common anaesthetic to be used for BSP was in 102 (51%) patients. Mean hours after which BSP achieved was 38.84 ± 47.65 hours , median 24 hours (Data from 164 pts) .CSF / Serum Autoimmune markers were positive in 28 patients (14%)–NMDA - 17 (8.5%),

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GAD – 7 (3.5%) , VGKC -1 (0.5%), Anti TPO – 2(1%), Zic 4 antibody – 1 (0.5%). Mean number of cycling of anaesthetics was 3.38 ± 2.41 , median - 3(0-12) hours . At discharge 80 (40%) had a bad outcome and 19.5 % of patients succumbed to the illness

Demographics, clinical, electrophysiological, radiological profiles profile of patients with SRSE is given in Table 1

Predictors of outcome of SRSE by univariate analysis

Univariate analysis was done for assessing the outcome of various variables and the following variables showed statistical significance

- i) STESS score: The mean STESS score analysed among SRSE patients at presentation was 2.8 ± 1.65 score being significantly lower in patients with good outcomes versus bad (2.98 ± 1.19 versus 2.73 ± 1.22 , $p=0.137$). A STESS score > 3 did not predict any bad outcome [79 (65.8%) versus 53(66.3%)]
- ii) Duration of ICU stay: The mean average duration of ICU stays in days was 27.21 ± 36.54 , significantly lower in patients with bad outcomes versus good outcomes (19.69 ± 17.17 versus 32.22 ± 44.42 , $p - 0.017$).

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iii) Duration of ventilator support: The mean duration (days) of ventilator support was 19.75 ± 28.95 days, lower in patients with bad outcomes versus good outcomes (13.1 ± 12.21 versus 24.18 ± 35.4 , $p=0.08$).

iv) EEG findings: Lateralised periodic discharges (LPDs) were seen in [n=143 (%), $p=0.918$], non-convulsive status epilepticus (NCSE) in [134 (67%), $p=0.086$], After status epilepticus ictal discharges (ASIDs) [n=116 (58%), $p=0.030$] and Burst-suppression Pattern (BSP) in [129 (64.5%), $p=0.09$] patients

v) Delay in starting anesthesia: Mean delay in starting anaesthesia 13.23 ± 23.58 hrs , median of 3 hours .The delay (hours) in starting anesthesia > 24 hour was in 36(18%) and was higher in patients with bad outcome versus good outcome 26(32.5%) vs 10(8.3%) $p < .001$

vi) Delay in starting immunotherapy in NORSE: The mean delay (days) in starting immunotherapy was 54.18 ± 25.59 hrs , median of 48 hrs , Immune therapy delay more than 48 hours was seen in 43(38.4%) patients , , significantly lower in patients with good outcomes versus bad outcomes (14 (76.3%) versus 29 (18.9%), $p<0.001$).

vii) Mean number of ASM was 5.71 ± 2.5 , median -5 (1-14) and Mean number of anaesthetics was 2.07 ± 0.98 , median 2. Use of > 5 ASM was seen in 77(38.5%) patients, higher in patients with good outcome versus bad outcome (56(46.7%) vs 21(26.3%), $p = .004$). Use of > 2 Anaesthetics was seen in 60 (30%)

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patients, higher in patients with good outcome versus bad outcome (43(35.8%))
vs 17(21.3%) , p- 0.027)

Age, gender, prior comorbidities, semiology of SE, EEG findings other than the ones mentioned above, CSF or MRI were not significant predictors of outcome in SRSE.

Details of treatment variables are enlisted in Table 2

SI NO	VARIABLES	GOOD OUTCOME	BAD OUTCOME	OVER ALL	P VALUE
1	Immunotherapy given	73 (60.8%)	38(47.5%)	111(55.5%)	.063
2	Need for vasopressors	93 (77.5%)	38(47.5%)	131(65.5%)	.001
3	Total Number of cycling's of anaesthetics				0.244
	≤5	89(74.2%)	65(81.3%)	154(77%)	
	>5	31(25.8%)	15(18.8%)	46(23%)	
4	Delay in starting anesthesia < 24 hour	110 (91.7%)	54(67.5%)	164(82%)	<.001
	> 24 hour	10(8.3%)	26(32.5%)	36(18%)	
5	Number of anesthetics				0.027
	≤2	77(64.2%)	63(30%)	140(70%)	
	>2	43(35.8%)	17(21.3%)	60 (30%)	
6	Number of ASM				.004
	≤5	64(53.3%)	59(73.8%)	123(61.5%)	
	>5	56(46.7%)	21(26.3%)	77(38.5%)	
7	Immunotherapy Delay				<0.001
	Within 48 hours	60(81.1%)	9(23.7%)	69 (61.6%)	
	> 48 hours	114(18.9%)	29(76.3%)	43(38.4%)	

Table 2; Treatment Variables of patients with SRSE

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Predictors of outcome of SRSE by multivariate analysis

Multivariate analysis showed acute symptomatic etiology (P-0.024) and delay in starting anaesthetics (P- < .001) as predictors of bad outcome. Burst suppression with anaesthetics (P- 0.036) and need for vasopressors (P-0.004) was associated with good outcome (**Table 3**)

VARIABLES	OR	CI	P Value
Etiology			
Acute symptomatic	2.48	1.13 – 5.47	0.024
Remote	0.74	0.24-2.27	0.59
Progressive	0.97	0.30 – 3.07	0.95
Duration of ventilator stay	0.981	0.96 – 1.00	0.053
BSP with anaesthetics	0.473	0.24 – 0.95	0.036
Need for vasopressors	0.36	0.18 – 0.72	0.004
Delay in anaesthetics	5.30	2.16 – 12.99	< 0.001

Table 3 – Multivariate analysis of patients with SRSE

7. DISCUSSION

Ours is a multicentre study focussing about 200 SRSE patients managed from 2011 to 2021 in various centres across India. Various retrospective studies have documented a prevalence of 12.2 – 22 % of SRSE among SE patients (5 , 6, 7). In a recent population-based survey , during 2008 to 2013, 338 out of 2,585 (13%) patients with SE had SRSE . This study also focussed about the financial burden of SRSE patients in Germany to the health system (8). In one retrospective study incidence of super refractory status epilepticus was found to be 0.7 per 100000 (7). Our Multicentre study showed 9.1 %(200 / 2196) SRSE patients among SE cohort which is similar to other various studies.

SRSE as an entity is quite common among younger patients and males were affected more often which has been also established in prior studies including our study (3,9). Prior seizures was the most common comorbidity which was seen in 21.5 % and none of them had any positive family history of SRSE. De novo origin of SRSE happens in majority as they lack any previous precipitating injury or prior comorbidities before SRSE sets in. Mechanism of establishing SRSE is poorly understood and are complex and multifactorial. This is likely explained by intensified “receptor trafficking,” in which the number of glutamatergic receptors at the cell surface increases and the number of GABA receptors decreases (10, 11, 12), leading to a reduction in GABA ergic activity. There are likely many other mechanisms contributing to the development of RSE and SRSE, which

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include (1) mitochondrial failure or insufficiency (13), (2) inflammatory processes (14, 15) resulting in decreased integrity of the blood–brain barrier and higher potassium levels (16, 17), and (3) changes in gene expression (18).

SRSE is likely following acute brain insult rather than chronic epilepsy and is more likely after central nervous system (CNS) infection, stroke, Auto Immune Encephalitis (AIE) or in a healthy brain with new onset refractory status epilepticus (NORSE) (19). Infections can also complicate SE and are associated with a poor outcome (20). The etiology of SRSE in the developing countries is dominated by CNS infections (9). Acute symptomatic etiology remains the most common in our study similar to many studies published (21, 22) and among acute symptomatic most common being AIE. NORSE is defined as a refractory status epilepticus without acute or active structural, toxic or metabolic cause. FIRES, is a subgroup of NORSE preceded by a febrile illness between 2 weeks and 24 h before the onset of RSE (23) NORSE was seen in about 116 (58%) patients of which FIRES comprises about 43 patients and being either of those didn't predict any outcome .Autoimmune causes are considered to be one of the major causes of NORSE (24).

Focal onset seizures (58%) are the most common seizure semiology and a focal onset ictal correlate has been seen in majority of our patients. Development of RSE or SRSE was associated with stupor or coma on admission and absence of

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history of epilepsy. These patients had a worse outcome compared to those who responded to AEDs (9, 21, 25). However in our study NCSE in coma has no relevance regarding the outcome. An increasing age was associated with worse outcome in many studies (22, 25) but age and sex in our cohort had no effect in outcome. A STESS score (>3) is a prognostic marker in case of SE in many studies (25), however it did not predict any outcome in our cohort of SRSE patients.

Acute encephalitis is one of the most important cause for acute symptomatic SRSE (27) and 14 % of patients were seropositive for AIE. CSF study to look for CSF pleocytosis and CSF or serum auto immune markers should be done in all patients with SRSE, however CSF examination was only done in about 60 % of our samples and only 55 % received any forms of immunotherapy. These factors should be addressed by the treating physician as it is already proven that any delay in immunosuppressant therapy adversely affects the outcome (3, 23). Duration of ventilator stay or hospital stay was much shorter in patients with bad outcome. Number of Anti-Seizure Medications and anaesthetic agents, need for vasopressors were also lesser in patients with bad outcome. This was contrary to the previous studies so far (3, 8) and one of the reason being patient with poor prognosis may have succumbed to the illness quite early and patient with good outcome had the chance for getting the benefit out of them.

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Intravenous Anaesthesia without delay was one of the most important predictors of outcome (3, 23) and Midazolam continued to be the preferred agent in our study (3). Anaesthetic agents have tachyphylaxis i.e. the effect goes down while continuing and these requires dose titrations and have to recycle its use (28). However prolonged recycling's (> 5) has no role in predicting the outcome in our study . But contrary to the results, cycling's of anesthetics continues to be in treatment protocol of SRSE and is logical. One of the target of anaesthetic use in refractory seizures is achieving burst suppression (29).Burst suppression has achieved in 64.5% of total patients only, BSP with anesthetics is associated with good outcome as expected. The mean delay in starting anaesthesia which is the gold standard in controlling such seizures was about 13 hours and hence this should be addressed particularly in the setting of our study in a developing country. Majority of the patients will reach a primary health centre and decision for prompt referral and early diagnosis of SRSE should be made from the clinician. Studies clearly shows early anaesthetics as early as possible preferably within 24 hours should be the target and this has to be included in the protocol (23)

SRSE is associated with higher morbidity and mortality even in developed countries. Case fatality rate in our study was 19.3 % and about 40 % had poor outcome. Interestingly majority of the deaths are due to treatment related

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complications and should be particularly cautious regarding the use of anaesthetic agents due to its cardiac depressant effect (30) .Another aspect is to reduce the prolonged hospital stay and to initiate early weaning strategies. Neuro rehabilitation in such patients should be done early and this is one area we didn't focus in our study

8. LIMITATIONS

There are many strengths to our study as this is the largest sample size and the first multicentre study so far published dealing SRSE . We were able to predict risk factors for both good and bad outcome. In our study we incorporated patients from a time period when SRSE became a reality known for and thus trying to bring forth a uniform protocol in treating patients. However the limitation was of the retrospective design we have used and systematic variations that can occur due to the multicentre model.

9. CONCLUSION

Etiology plays an important role in the outcome of SRSE, hence identifying the etiology and early symptomatic treatment is essential. Delay in starting Anaesthesia is considered to be an important predictor for poor prognosis. Burst suppression should be the target for SRSE therapy. Auto immune encephalitis is an emerging etiological factor for SRSE as documented in 14 % of patients and immunotherapy for SRSE patients has been tried only for 55 % addressing the

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deficit and need for an effective protocol implementation . Medical complications should be addressed during the prolonged ICU stay. Early diagnosis, prompt referral and protocol driven treatment is essential for managing these patients

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ANNEXURES

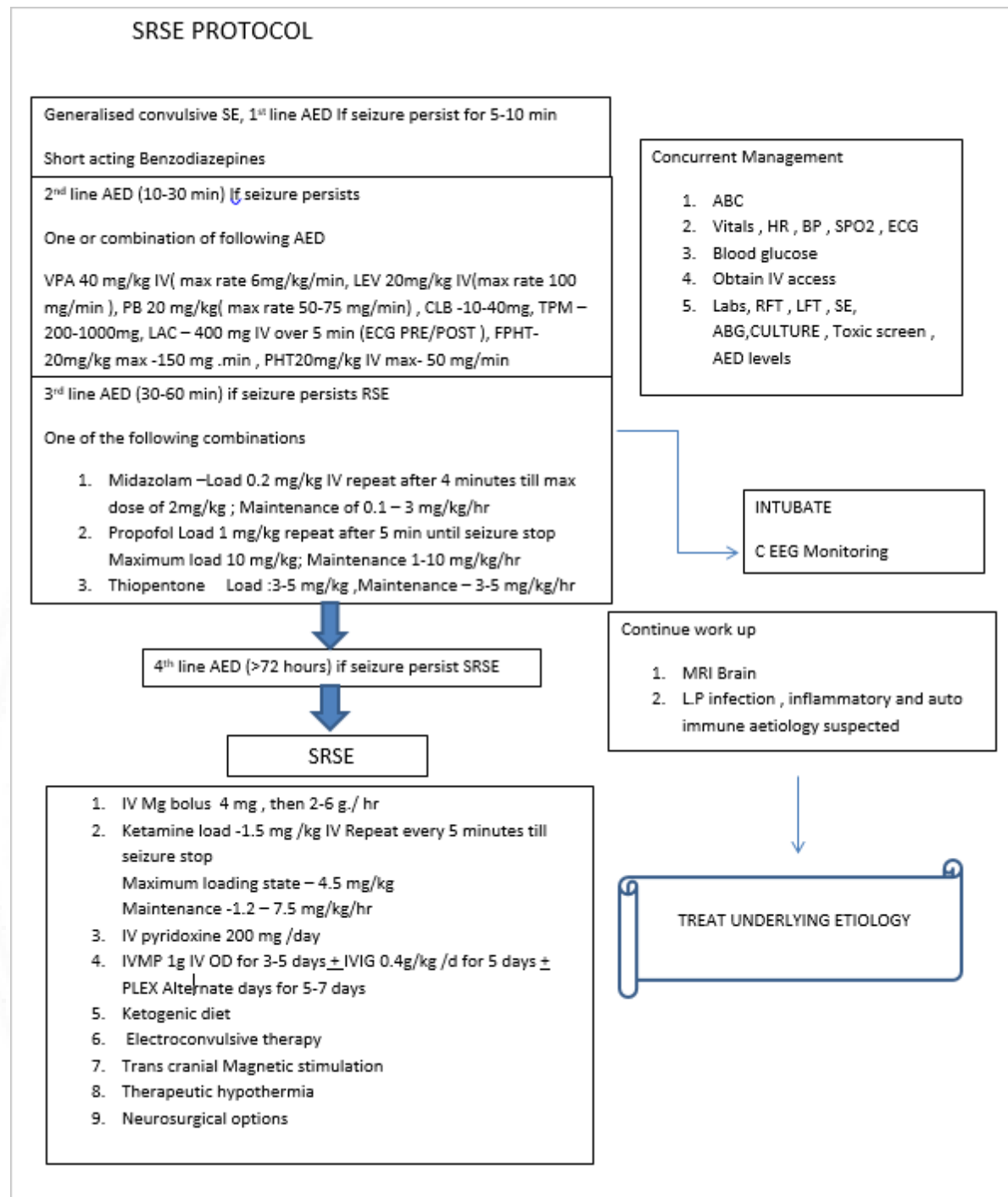
1. STESS SCORE

Consciousness	Alert or confused	0
	Stuperous or comatose	1
Worst seizure type	Simple partial ,	0
	CPS , Absence	1
	Generalised	2
	NCSE	
Age	<65	0
	>65	2
History of previous seizures	Yes	0
	No	1
Total		0-6

2. GLASGOW OUTCOME SCORE

GOS Score	Interpretation
1	Death
2	Vegetable state
3	Severe disability
4	Moderate disability
5	Good recovery

3. SRSE PROTOCOL



4. Recent studies depicting the incidence, aetiology, outcome of refractory and Super Refractory Status Epilepticus

Study group, study period, number of centres, country	Number of patients of SE % of RSE /SRSE	Outcome	comments
Hassan et al , 10 years , 1 , india	N-84 21 % RSE , 7%SRSE	Seizures controlled in in 69.6% of RSE Seizures uncontrolled in 88% SRSE	Acute symptomatic aetiology , time delay to treatment , old age and altered sensorium to admission predicts poor outcome
Jayalekshmi et al , 10 years , 2 , india	N- 177 40.7% RSE 16.7% SRSE	40% Mortality and 33.3% good outcome in SRSE 35.7% mortality and 57.1 % good outcome in RSE	Encephalitis most common aetiology in 1/3 rd RSE and 2/3 rd SRSE
Misra et al , 3 Years , 1 , india	N- 107 13% SRSE	43 % Mortality in SRSE	SRSE Patients with treatable aetiology has better outcome
Giovannini et al , 1 year , 1 Italy	N- 83 14% RSE 17% SRSE	54% Mortality in SRSE at 30 days , 19% returned to base line status	Coma at presentation and acute symptomatic aetiology predicted SRSE and RSE.Incidence higher than other studies
Kantanen et al , 3 years , 15 , Finland	N- 395 78% RSE 22% SRSE	36% Mortality in SRSE and 22 % in RSE	Incidence is 5-10% of all SE (0.7 /100000)
Delaj et al ,10 years, 1, Switzerland	N- 804 33.3% RSE 4% SRSE	37.9% Mortality in SRSE , 24.5% mortality in RSE	Coma lack of remote symptomatic etiology and increasing age correlated with RSE , Coma , younger age correlated with SRSE
Tian et al , 3 years,1 china	N- 98 20.4% RSE 12.2% SRSE	50% Mortality in SRSE	67% SRSE due to viral encephalitis and <10% had preexisting epilepsy

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5 . Table 1 showing Demographics, clinical, electrophysiological, radiological profiles profile of patients with SRSE

SI NO	VARIABLES	GOOD OUTCOME	BAD OUTCOME	Overall	P value
1	AGE	35.14 $\pm$ 31.38	32.68 $\pm$ 24.22	34.145 $\pm$ 28.69	0.554
2	GENDER Females Males	49 (40.8 %) 71(59.2%)	34 (42.5 %) 46 (57.5 %)	83 (41.5 %) 117 (58.5 %)	0.815
3	PRIOR COMORBIDITIES Stroke 8(4%) Trauma 9(4.5%) Seizures 43 (21.5%) No seizures	25(21.3%) 83(76.9%)	18(24%) 57(76%)	43(23.5%) 140 (76.5 %)	0.894
4	ETIOLOGY Acute Symptomatic Remote Symptomatic Progressive Cryptogenic	43 (35.8%) 18(15%) 14 (11.7%) 45(37.5%)	45 (56.3%) 8 (10%) 7(8.8%) 20(25%)	88 (44%) 26(13%) 21 (10.5%) 65(32.5%)	0.043
5	FIRES NORSE	49(40.8%) 72(60%)	22(27.5%) 44(55%)	71(35.5%) 116(58%)	0.054 0.483
6	SE TYPE Focal Generalised / unknown	69(57.5%) 51(42.5%)	47(58.8%) 33(41.3%)	116 (58%) 84	0.861
7	STESS SCORE ≤ 3 >3	79(65.8%) 41(34.2%)	53(66.3%) 27(33.8%)	132(66%) 68(34%)	0.951
8	DURATION OF VENTILATOR STAY	24.18 $\pm$ 35.4	13.1 $\pm$ 12.21	19.75 $\pm$ 28.95	0.08
9	DURATION OF ICU STAY	32.22 $\pm$ 44.42	19.69 $\pm$ 17.17	27.21 $\pm$ 36.54	0.017
10	CSF Abnormal	25(20.8%)	16 (20%)	41(20.5%)	0.547
11	MRI Normal Abnormal	36(30%) 84(70%)	33(41.3%) 47(58.8%)	69(34.5%) 131(65.5%)	0.101
12	Ictal onset Focal onset uni Focal onset Multi (U/L) Focal onset multi (B/L) Diffuse onset	28(23.5%) 31(26.1%) 26(21.8%) 34(28.6%)	19(24.5%) 13(16.5%) 24(30.4%) 23(29.1%)	47(23.7%) 44(22.2%) 50(25.25%) 57(29.1%)	0.341
13	Periodic discharges LPD BPD GPD No discharges	27(22.5%) 30(25%) 28(23.3%) 35(29.2%)	18(22.5%) 18(22.5%) 22(27.5%) 22(27.5%)	45(22.5%) 48(24%) 50(25%) 57(28.5%)	0.918
14	NCSE	86 (71.7%)	48(60%)	134(67%)	0.086
15	After SE discharges	77(64.2%)	39(48.8%)	116(58%)	0.030
16	BSP with anaesthetics	83 (69.2%)	46 (57.5%)	129(64.5%)	0.09

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16	Post ictal changes	27 (22.5%)	25 (31.3%)	52(26%)	0.051
	Focal Slowing	42 (35%)	27(33.8%)	69(34.5%)	
	Diffuse slowing	5 (4.2%)	5(6.3%)	10(5 %)	
	Focal attenuation	23 (19.2%)	11(13.8 %)	34(17%)	
	Diffuse attenuation	11(9.2%)	0(%)	11(5.5%)	
	No seizure control	12(10%)	12(15%)	24(12%)	
	Normal				
17	IED	49(41.2%)	29(37.2%)	78(39.6%)	0.721
	Focal	45(37.8%)	34(43.6%)	79(40.1%)	
	Multifocal	25(21%)	15(19.2 %)	40(20.3%)	
	Generalised				



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(IEC Regn No. ECR/189/INS/AL/2013/IKK-21)

SCT/IEC/1934/AUGUST/2022

03.09.2022

Dr. Ashalatha R
Professor
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Ashalatha,

The Institutional Ethics Committee held on 20th August, 2022, reviewed and discussed your application to conduct the study titled "PREDICTION MODEL FOR OUTCOME OF PATIENTS WITH SUPER REFRACTORY STATUS EPILEPTICUS –MULTI CENTRE STUDY " (IEC/1934).

The following members of the Ethics Committee were present at the meeting held on 20th August, 2022

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
5.	Dr. Rejish Kumar	MBBS,MD, DNB	Male	Clinician	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Adv. N Anand	BAL, L.L.B	Male	Legal Expert	No
8.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
9.	Dr. Hankrishna Varma PR	Ph.D (Materials Science)	Male	Medical Technology	Yes
10.	Dr. Manikandan S	MBBS,MD,PDCC	Male	Clinician	Yes
11.	Dr. Narayanan Nambodiri. K.K	MBBS,MD,DM	Male	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

1. Checklist Form
2. Study Proposal
3. IEC Application Form
4. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 02.03.2022
5. CV of PI and Co-PIs
6. Covering letter addressed to the Director, SCTIMST dated 31.08.2021
7. Data Sharing Agreement
8. Forwarding letter from HOD
9. Reply to the comments
10. Declaration form
11. Responses/Amendments made based on the Reviewer's Comments
12. SRC Recommendation letter

IEC Decision

The IEC approved the conduct of the study in the present form.
Confidentiality of Personal data is to be ensured.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,


Dr. G. Srinivas
Member Secretary, IEC



ABBREVIATIONS

ILAE – International League Against Epilepsy

NORSE- New Onset Refractory Status Epilepticus

FIRES – Febrile Infection Related Epilepsy Syndrome

SRSE –Super Refractory Status Epilepticus

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RSE – Refractory Status Epilepticus

SE – Status Epilepticus

LPDs- Lateralised Periodic Discharges

PLEDs - Periodic Lateralised Epileptiform Discharges

NCSE - Non-Convulsive Status Epilepticus

ASIDs - After Status Epilepticus Ictal Discharges

sBSP- Spontaneous Burst-Suppression pattern

STESS Score - Status Epilepticus Severity Score

91%
Unique Content

9%
Plagiarized content

✓ COMPLETED
100%

Sentence wise results

Matched URLs

Super refractory status epilepticus (SRSE) is an important neurological emergency.

It is defined as status epilepticus that continues for more than 24 hours despite ...

It was a term first used in third London Innsbruck colloquium on status epilepsy h...

In many studies it is found that this condition is associated with significant mort...

Majority of the times SRSE occurs de nova in a healthy brain without any prior his...

We conducted a retrospective study from our own institute regarding the predictors...

in SRSE and were able to identify the predictors of outcome and has been published.

The prognosis in SRSE was not dismal as thought of and a good planned protocol is ...

However there are no multicentre trial and Randomised controlled trial so far avai...

In this study we want to study the predictors of outcome in SRSE recruiting much l...

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