# SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA


# ELECTRO-CLINICAL AND RADIOLOGICAL PREDICTORS OF OUTCOME IN SUPER REFRACTORY STATUS EPILEPTICUS

Thesis submitted in partial fulfilment of the rules and regulations for DM Degree

Examination of

Sree ChitraTirunal Institute for Medical Sciences and Technology


By

**Dr. Jithu Jose**

DM Neurology Resident


Month and Year of Submission: July 2021


Department of Neurology

Sree Chitra Tirunal Institute for Medical Sciences and Technology Thiruvananthapuram


2019-2021

# DECLARATION

I, Dr. Jithu Jose, hereby declare that this project titled 'Electro-Clinical and Radiological predictors of outcome In Super Refractory Status Epilepticus' was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram,

Date: 30-07-2021.

Dr. Jithu Jose

DM Neurology Resident

## Forwarded:

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.

Thiruvananthapuram,

Date: 30-07-2021

Dr. Ashalatha Radhakrishnan

Professor of Neurology

Epileptologist, (RMNC)

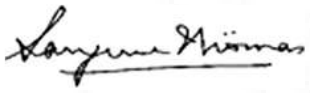
In charge comprehensive centre for sleep disorders

Department of Neurology,

SCTIMST.

## Forwarded:

The candidate, Dr. Jithu Jose, has carried out the project titled 'Electro-Clinical and Radiological predictors of outcome In Super Refractory Status Epilepticus' as part of the minimum required project.



Thiruvananthapuram,

Date: 30-07-2021

Dr. Sanjeev V. Thomas,

Professor (Senior Grade) and Head,
Department of Neurology,
SCTIMST.

**ACKNOWLEDGEMENT**

I take this opportunity to express my sincere gratitude to **Dr. Ashalatha Radhakrishnan,** Professor of Neurology, Department of Neurology, SCTIMST, my guide for the study, for her expert guidance, constant review, kind help and keen interest at each and every step of the study. I am grateful for **Dr Sanjeev V Thomas**, HOD department of Neurology, **Dr Ramshekhar Menon** , **Dr Ajith Cherian** and **D**r **Sajith S. Sukumaran** for their valuable inputs into the study

I am grateful to **Dr. Keni Ravish** and **Dr. Haseeb Hassan**, for their assistance and valuable inputs. I express my sincere thanks to **Dr. Ravi Prasad Varma. P**, Associate Professor, Achutha Menon Centre for Health Science Studies for providing valuable inputs regarding the statistical analysis of this study.

I am thankful to the entire faculty, nursing staff in Epilepsy unit, and my colleagues for their valuable input and assistance to the study.

Last but not the least, I extend my gratitude to all my patients and their primary caregivers who participated in this study, without whose cooperation this study would not possible.

Dr. Jithu Jose

# INDEX

# SYNOPSIS

## SYNOPSIS

**Purpose:** We conducted this study to determine the clinical, electrophysiological and radiological predictors of outcome in Super Refractory Status Epilepticus (SRSE).

**Methods:** Data of patients treated for SRSE between January 2000 and November 2019, archived prospectively in our SE registry was analysed. Functional outcome was measured by Glasgow outcome score (GOS) at the time of hospital discharge and was divided into: good i.e. GOS≥3 and bad outcome i.e. GOS<3. The predictors of outcome were determined using appropriate statistical tests by univariate and multivariate analysis, $p<0.05$ was considered as statistically significant.

**Results:** Of the 384 patients with status epilepticus (SE) identified during the study, 28 were (8%) diagnosed as SRSE and were included in the final analysis. The mean age of the study population was 18.82 +20.45 years. 19 (67.9%) were males and 9(32.1%) were females. Acute symptomatic [n= 15 (53.5%)] was the most common etiology of SRSE. 12 patients (42.9%) had good outcome and 16 patients (57.1%) had bad outcome. Multivariate logistic regression analysis showed that independent predictors of poor outcome were: duration of ICU stay ($p<0.001$); EEG findings such as NCSE in coma (0.032), sBSP (0.001) and

post-ictal diffuse attenuation (<0.001); delay in starting anaesthesia (0.002); and delay in starting immunotherapy in NORSE (0.002). Neuroimaging findings did not affect the outcome. DTI studies which was available in 14 out of 28 patients showed diffuse white matter tract involvement when compared with the controls.

**Conclusion:** We could determine independent therapeutic and electrophysiological prognostic factors for SRSE. A uniform protocol driven management of SRSE can result in good outcomes in more than one-third of cases.

# INTRODUCTION

## 1. INTRODUCTION

American Epilepsy Society Working Group on Status Epilepticus (SE) in 1993 defined SE as seizures that last for more than 30 min or occurrence of two or more seizures without recovery of consciousness in between. Often seizures will cease within one minute or two if seizures become prolonged beyond a few minutes, it can cause irreversible neuronal injury, and hence 5 min duration is now considered as SE.

Up to 40 % of status epilepticus episodes do not respond to first- and second-line therapy (Refractory SE, RSE) and may require anesthetics for control of seizures by achieving therapeutic coma (1). Seizures can continue even after induction of coma, 10-15% of all SE episodes and they do so after more than 24 h of continuous anesthetic therapy or recur on reduction or withdrawal of anesthetic agents. The resulting condition, according to a recent definition was coined super-refractory SE (SRSE) at “Third London – Innsbruck Colloquium on Status Epilepticus held at oxford 2011” (2). The overall available data on this extreme variant of SE is limited (3, 4). The incidence of SRSE is estimated to be between

4% and 22% of all the patients with SE in various studies. On the other hand, data on mortality and functional outcome vary significantly and have been reported to be ranging from death to even good functional recovery (4, 5). Therapeutic decision-making in SRSE is challenging, especially in extremely long episodes in which the question of how long to maintain therapy is still debated (5). Therefore, the primary goal of this study was to assess the predictors of the outcomes in SRSE. Autoimmune Encephalitis (AIE) is now considered to be an emergent cause for RSE and SRSE and this study explores the complex interplay between infectious and autoimmune aetiologies which helps to identify the role of AIE in SRSE.

# REVIEW OF LITERATURE

## 2. REVIEW OF LITERATURE

SRSE usually follows acute brain injury insult and is more symptomatic rather than chronic epilepsy. It occurs with central nervous system (CNS) infection, stroke, or can occur de nova in a healthy brain with new-onset refractory status epilepticus. SE can evolve into refractory status epilepticus (RSE) and one Indian study found that acute SE Etiology, coma/stupor at presentation, and serum albumin <3.5 g/l were the more common predictors (6). Stupor or coma on admission and absence of a history of epilepsy was associated with the development of RSE or SRSE. These patients had a worse outcome compared to those who responded to AEDs (7). Infections can also complicate SE and are associated with a poor outcome (8). The etiology of SRSE in developing countries is dominated by CNS infections (9). SRSE can be convulsive or non-convulsive. Myocardial injury, aspiration pneumonia, pulmonary edema, and rhabdomyolysis leading to renal failure are the common complications seen with convulsive SE. Recurrent Non-convulsive Status Epilepticus (NCSE) is considered to be a bad prognostic marker and often SRSE patient requires continuous electroencephalography (EEG) monitoring. SE may occur due to failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms leading to prolonged seizures (t1).

Seizures that persist for a long time can result in neuronal injury, neuronal death, and alteration of neuronal network and can cause long-term sequelae (after time point t2). For convulsive SE, t1 time is taken as 5 min and t2 time as 30 min. For non - convulsive types of seizures, t1 and t2 are not known (10). Status epilepticus is broadly defined as a seizure activity that continues for 30 min or recurrent seizures without recovery between attacks. Experimental evidence suggests that irreversible neuronal injury may start after 20 to 30 min of generalized convulsive status epilepsy (16). So every effort has to be made to stop seizure activity before that phase.

There are no multicentre trials or Randomised trials available with regards to SRSE and data are available from retrospective case series studies only. From China, 13 patients with SRSE were reported during January 2010 to August 2013 (11); from France, 78 SRSE patients were included in a survey from 2001 to 2011 having SE more than 7 days of anesthesia (12), and from South India (Hyderabad) 30 (16.9%) patients, and from Vellore 17 (7.7%) events of SRSE were reported (13, 14). In a recent population-based survey from Germany, from 2008 to 2013, 338 out of 2,585 (13%) patients with SE had SRSE (15). In Kantanen et al retrospective study of 3 year duration from Finland, the incidence of SRSE was found to be 5 to 10% of all status epilepsy(.7 per 100000) (17)

Super refractory status epilepsy 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. Yaohua Li et al study of 13 SRSE Patients in West China Hospital, Sichuan University, between January 2010 and August 2013, was retrospectively analyzed. The outcome was measured using Glasgow Outcome Scale (GOS) at discharge, at three-month and long-term follow-ups. The demographic pattern suggests more patients with younger age and majority (61.5%) had encephalitis as etiology. In-hospital mortality at the time of admission was 15.4% (2/13), and three-month mortality was 36.4%. 18.2% of patients improved and 45.5% patients had good recovery at long-term follow-up. Older age patients with multiple comorbidities had higher mortality compared to the younger age patients. For survivors, functional outcome had significantly improved at three-month follow-up (GOS score = 4.1 1.2) when compared to that at discharge (GOS score = 3.1 1.2, $P < 0.05$). Long duration of anesthesia, etiology of encephalitis, and positive neuroimaging findings tended to be associated with poor functional outcomes. (11)

## How do seizures become refractory?

Seizures are sustained by either imbalance of neuronal excitation and inhibition or failure of normal inhibitory mechanisms [18]. γ-Aminobutyric acid (GABA) neurotransmitter by its inhibitory mechanism prevents neuronal excitation by activation of the GABA receptor, and glutamate mediates excess excitation via the N-methyl- D-aspartate (NMDA) receptor. In many experimental and clinical studies after 30 minutes of recurrent seizures, seizures become self-sustaining with the establishment of new circuits and can result in neuronal damage after 30 min of continuous seizure activity [19–23]. Benzodiazepines an agent extremely helpful in the initiation phase develop pharmacoresistance as SE continues [20], and in the later course, NMDA receptor blockers like ketamine can be effective in the maintenance course of SE [24]. There is an internal intensified "receptor trafficking," in which the number of GABA receptors decreases and subsequently glutaminergic receptors at the cell surface increases [25–27], which leads to reduced GABAergic activity. There are likely many other mechanisms contributing to the development of RSE and SRSE, which include (1) mitochondrial failure or insufficiency [28], (2) inflammatory processes [29, 30] resulting in decreased integrity of the blood-brain barrier and higher potassium levels [31, 32], and (3) changes in gene expression [33].

## Evaluation of the patient with Refractory and super refractory seizures

### CSF Analysis

CSF analysis is a must in the case of SE particularly without an unidentified cause, immunocompromised patients, and also in patients with a history and/or examination findings suggestive of central nervous system (CNS) infection. Routine studies depending on the age, comorbidities, and social history of the patient should be done as early as possible before starting immunomodulatory therapy and needs to rule out CNS infection. If still, the cause is unclear, additional CSF analysis should be done including CSF cytology and a complete CSF autoimmune panel. A Comprehensive paraneoplastic panel and Tumour workup also should be considered when there is radiological evidence of limbic encephalitis and also in elderly patients with refractory SE.

### EEG as a tool in Refractory seizures

For monitoring SRSE, a continuous EEG is mandatory. It will help in the detection of NCSE, manage seizures, and should be initiated within 1 h of the onset of SE.

EEG is also helpful in Auto-Immune Encephalitis like NMDA receptor encephalitis which has characteristic EEG patterns like extreme delta brush. Continuous EEG monitoring is also mandatory during anesthetic use as it should be titrated until the cessation of all electrographic seizures and/or achieving

burst-suppression patterns. Maintaining burst suppression pattern (BSP) is challenging as seizures can also occur at this phase and hence to be monitored. It is uncertain whether this seizure will add onto the neurological worsening, hence an additional escalation of anesthetics to achieve an isoelectric state is unwanted. BSP is routinely maintained for 24 hours followed by slow tapering of anesthetics while monitoring recurrence of seizures. EEG often will fail in clearly differentiating between ictal and inter ictal patterns and may not be straightforward in usual settings. Many patients will have Periodic discharges (either lateralized or generalized), and often they fluctuate and evolve in between and can be superimposed with fast or rhythmic activity. This makes it difficult in distinguishing between ongoing SE and the transition to the inter ictal or post ictal state.

**MRI in SRSE**

Brain imaging findings in affected patients have been reported in few case series and some case reports. 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. Basal ganglia and temporal lobes are the more common sites showing flair hyper intensities and rarely it can occur in the brainstem and thalamus too. In the acute phase of SRSE, certain minority patients will have

diffuse cerebral edema and such patients have bad outcomes with increased mortality.

Diffuse cerebral atrophic changes and mesiotemporal sclerosis are often seen in the chronic phase of SRSE. However, none of the studies till now clearly shows a specific MRI pattern as a prognostic marker. An understanding of these MRI abnormalities is necessary to support the diagnosis of SRSE and exclude mimics

**MRI - DTI and Fractional Anisotropy**

Diffusion tension imaging (DTI) can be used to measure anisotropy per voxel and provides the directional information relevant for magnetic resonance tractography. DTI has become a useful tool for the investigation of brain disorders such as dementia, stroke, epilepsy, brain tumors, and demyelinating and dysmyelinating disorders and it also allows the indirect examination of the brain microstructure. DTI enables the mapping and the orientation of white-matter tracts [60]. Diffusion is described by using the apparent diffusion coefficient (ADC) and is sufficient for pathologies in areas such as grey matter. The presence of anisotropy is measured in the white matter using a tensor D, which helps in describing the mobility of molecules in one particular direction and correlates between these directions. The tensor may be diagonalized such that 3 elements, called eigen-values, remain along the diagonal. Three eigenvalues — lambda 1, lambda 2, and lambda 3 are derived.

DTI allows clinicians to look at anisotropic diffusion in white-matter tracts, but it is limited in its ability to demonstrate spatial and directional anisotropy. The eigenvector corresponding to the largest eigenvalue termed the principal eigenvector, defines the main direction of diffusion of water molecules in that voxel. Mapping the principal directional eigenvectors in each of the voxels forms the basis for tractography. Apparent diffusion coefficient (ADC), is a measure of overall diffusivity irrespective of directional dependency; fractional anisotropy (FA), is a measure of the directionality of the molecular motion of water and is taken from eigenvalues as the normalized value of tensors degree of anisotropy. Altered diffusivity and disorganization of white matter tract can occur in many pathological conditions including RSE and it can lead to decreased anisotropy and this can be apparent even if routine MRI is normal and thus can be utilized in early detection of the cause

Values of FA and ADC may vary independently in a particular condition as it can be explained by the fact that damaged or malformed brain has glia and neurons, respectively. Therefore, they have enough cell density to prevent effects on ADC; however, because of the disorganization, FA is reduced.

SRSE is widely believed to be due to a diffuse molecular pathology and usually occurs as an acute insult. The majority of the patient had normal MRIs and hence in this study, DTI is utilized to identify hidden structural pathology.

There is a huge gap in understanding the disease entity as such with the absence of randomized controlled and multi-centric trials. Various studies has enlisted incidence and prevalence of SRSE , but outcome predictors specific to SRSE which has taken into account all the aspect is not available .Hence the plan of our study is to identify the electro – clinical radiological predictors of outcome and to format a uniform protocol for management of SRSE.

# AIMS AND OBJECTIVES

## 3. AIMS AND OBJECTIVES

The objective of our study is

1. To study demographical, clinical, EEG, and MRI (Structural and functional) profiles of patients with Super refractory status epilepticus

2. To assess the predictors of outcome in those patients at discharge and within 1 year of follow up

Thus these findings will help clinicians formulate treatment strategies to improve the outcomes of SRSE. Also, there are only very few studies addressing SRSE alone

# METHODS

# 4. METHODS

## 4.1 Definition of super-refractory status epilepticus

SE is defined as ongoing seizures without normalization of consciousness for at least 5 minutes or two or more discrete seizures between which there is incomplete recovery of consciousness (34). Refractory Status Epilepticus (RSE) is defined as SE resistant to one first line, and one-second line AED, requiring general anesthesia (35). Super-Refractory Status Epilepticus is defined as 'status epilepticus that continues 24 h or more after the onset of anesthesia, including those cases in which the status epilepticus recurs on the reduction or withdrawal of anesthesia.

## 4.2 Study population

The archived data of all cases treated from January 2000 until November 2019 from our SE registry, EMR OPD, and case records in our institute were reviewed and screened for episodes meeting the above-mentioned criteria for SRSE. Patients who met our inclusion criteria irrespective of age, sex, and ethnic state were selected. Patients with refractory Epilepsia Partialis Continua, Psychogenic epilepsy, and patients with SRSE who were treated elsewhere were excluded. The study was approved by the Institute Ethics Committee of the institute.

## 4.3 Collection of data

Our study is a single centre retrospective observational study from the largest tertiary care centre in India with catchment area including whole of India and neighbouring countries. Data of patients treated for SRSE between January 2000 and November 2019, was retrieved from our prospectively maintained SE registry, case records, discharge summaries and analysed. Patients who gets admitted with status epilepsy will be registered in our SE registry which is organised and maintained as Electronic Medical Records. Patients with the diagnosis of SE were included at the time of admission with the diagnosis electronically through coding. 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. The aetiologies 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 (36). A STESS score of 3 or more points was considered unfavourable and episodes were dichotomized accordingly (37, 38). 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.

Continuous EEG data recorded from all SE patients was retrieved from the compiled and stored data archived in hard drives and was re-read by primary investigator and co investigators first. This is to be checked by a Senior Epileptologist and Electrophysiologist with ample expertise in emergent EEG reading. The EEG findings is defined based on the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. NCSE is diagnosed based on modified Salzburg Consensus Criteria for diagnosis of Non-Convulsive Status Epilepticus. Data was by qualified electro physiologist and epileptologist right from day one of entry of the patient and throughout the period of stay of hospitalisation. So no NCSE should be missed since it is mandatory that each and every patient undergoes continuous EEG monitoring in the ICU. The epochs in our study is mandatory before induction of anaesthesia, during maintenance phase, in the weaning phase and during SE regression phases.

DTI data were retrospectively taken from available patients. FA and ADC will be analyzed using DSI software and it will be compared with an equal number of DTI data from normal patients which were already available in our registry retrospectively from the data base matched to the age, sex, and ethnic characteristics.

### 4.4 Outcome definition

Functional outcome was measured by Glasgow outcome score (GOS) at the time of hospital discharge and 1 year of discharge was assessed using the last available follow-up information from our records in the registry (39).Outcome was further divided based on GOS score : bad outcome <2(1,2 ) , better outcome > 3 (3,4,5 ) for statistical analysis.

### 5. Statistical analysis

Data were analyzed 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 comparisons were analyzed by univariate analysis. Numerical data were analyzed via T-test or Mann-Whitney U test and categorical data by Chi-square test and Fisher exact test. MRI DTI data was analysed by independent t- test. If p was <0.1 then multivariate analysis using logistic regression was done. A variable having a two-tailed p-value of < 0.05 was considered statistically significant. For those variables with few numbers and had difficulty in calculating statistical significance, we used Yates correction of the chi-square test.

# RESULTS

# 6. RESULTS

## 6.1 Study population

A total of 384 SE episodes were identified during the study period from January 2000-November 2019. Among those with SE episodes 38 were excluded from further analysis due to inadequate data, error in coding lost to follow up, and missed case records. So leaving 346 episodes of SE for the final analysis of which 40 patients (11.5%) had satisfied the criteria of RSE and 28 (8 %) patients were SRSE.

## 6.2 Demographic and clinical profile

The mean age of the patients in the study group was 18.82 +20.45, males were 68 %, while females were 32%. Thirty-two percent of patients had prior comorbidities among which prior history of seizures (25%) was the most common and none of the patient had a positive family history. SRSE was generalized or unknown in 20 (71.4%) and focal onset in 8 (28.6%) patients.

Etiologies 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 (15/28 –53.5 %) were the most common cause of SRSE followed by idiopathic 8 /28(- 28.5%),

remote symptomatic 2/28 (- 7.14%) and progressive symptomatic 3/28(- 10.7%), shown in (Figure; 1).

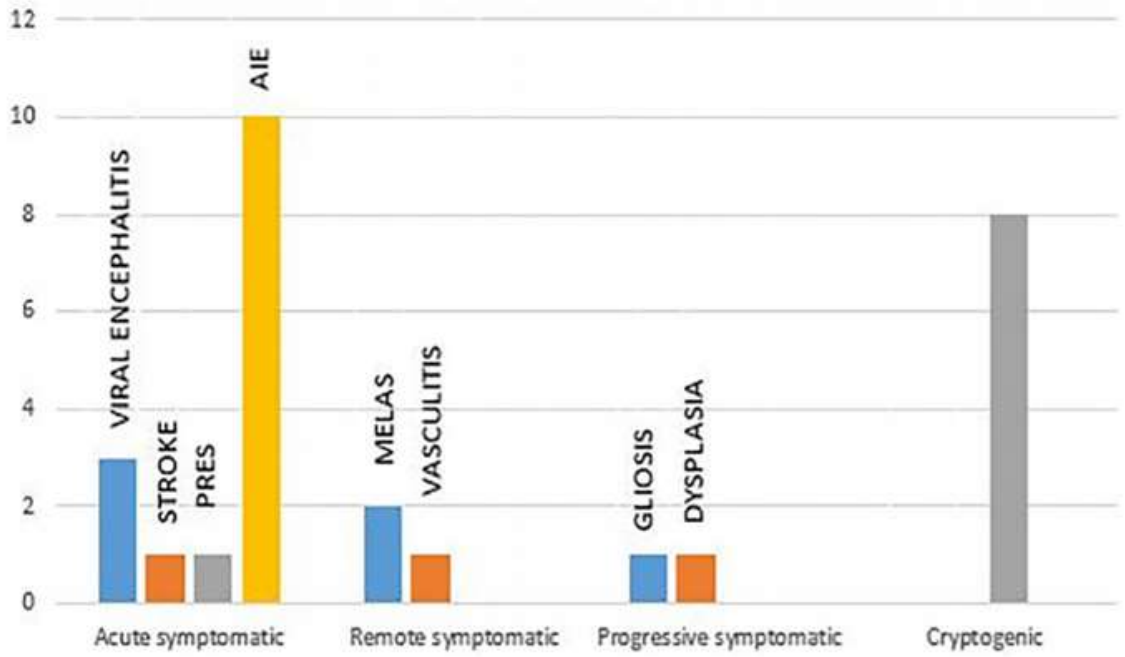



Figure 1 – Etiologies of SRSE, Abbreviations; PRES – Posterior Reversible Encephalopathy Syndrome , MELAS – Mitochondrial Encephalopathy Lactic Acidosis and Stroke like episodes

New-onset refractory status was seen in thirteen patients among which 3 patients had viral encephalitis, 6 patients had seropositive and 4 patients had seronegative autoimmune encephalitis. Febrile infection-related epilepsy syndrome (FIRES) was seen in five patients

| Table 1. Clinical, electrophysiological, radiological profile and predictors of outcome in SRSE | | | | |
|---|---|---|---|---|
| Variables | **Overall Value** | **Good outcome** | **Poor outcome** | **p Value** |
| Age in years (mean±S.D.) | 18.8 ±20.5 | 16.4 ±10.6 | 20.6±12.8 | 0.372 |
| Gender | | | | |
| *Males* | 19(67.9%) | 7(58.3%) | 12(75%) | 0.350 |
| *Females* | 9(32.1%) | 5(41.6%) | 4(25%) | |
| Comorbidities | | | | |
| Past history of seizures | 7 ( 25 % ) | 2 (16.7 %) | 5(17.9%) | 0.66 |
| Etiology | | | | |
| *Acute symptomatic* | 15(53.6%) | 7(58.3%) | 3(81.3%) | 0.887 |
| *Progressive symptomatic* | 3(10.7%) | 1(8.3%) | 2(12.5%) | 0.724 |
| *Remote symptomatic* | 2(7.1%) | 1(8.3%) | 1(6.3%) | 0.832 |
| *Cryptogenic* | 8(28.6%) | 3(25%) | 10(62.5%) | 0.82 |
| Status epilepticus type | | | | |
| Generalised or unknown onset | | | | |
| Focal onset | 20(71.4%) | 7(58.3%) | 13(81.3%) | 0.184 |
| | 8(28.6%) | 5(41.7%) | 3(18.7%) | |
| STESS Score | 2.3±1.1 | 2.2±0.4 | 2.8±0.8 | 0.025 |
| Duration of ICU stay (days) | 65.7±22.9 | 50.7±12.7 | 78.3±15.8 | <0.001 |
| Duration of ventilator support (days) | 43.9±16.8 | 38.7±8.3 | 47.5±9.1 | 0.014 |
| EEG findings | | | | |
| Periodic discharges | | | | |
| *LPDs* | 8(28.6%) | 1(8.3%) | 7(43.8%) | 0.040 |
| *BPDs* | 5(17.9% ) | 3(25%) | 2(12.5%) | 0.393 |
| *GPDs* | 15(53.6%) | 8(66.7%) | 7(43.8%) | 0.229 |
| NCSE in coma | 10(35.7%) | 1(8.3%) | 9(56.3%) | 0.001 |
| ASIDs | 11(39.3%) | 2(16.7%) | 9(56.3%) | 0.034 |
| Spontaneous BSP | 13(64.2%) | 2(16.7%) | 11(68.8%) | 0.006 |
| IEDs | | | | |
| *Focal* | 8(28.6%) | 3(25%) | 5(31.3%) | 0.717 |
| *Multifocal* | 11(39.3%) | 4(33.3%) | 7(43.8%) | 0.578 |
| *Generalised* | 9(32.1%) | 5(41.7%) | 4(25%) | 0.350 |
| Post-ictal background | | | | |
| *Normal* | 6 (21.4%) | 5(41.7%) | 1(6.3%) | 0.023 |

| | | | | |
|---|---|---|---|---|
| *Focal slowing* | 3(10.7%) | 1(8.3%) | 2(12.5%) | 0.724 |
| *Diffuse slowing* | 10(35.7%) | 6(50%) | 4(25%) | 0.172 |
| *Focal attenuation* | 3(10.7%) | 1(8.3%) | 2(12.5%) | 0.724 |
| *Diffuse attenuation* | 6(21.4%) | 0 | 6(37.5%) | <0.001* |

| Variables | **Value** | **Good outcome** | **Poor outcome** | **p Value** |
|---|---|---|---|---|
| CSF Changes | | | | |
| *Normal* | 13(46.4%) | 6(50%) | 7(43.8%) | 0.743 |
| *Lymphocytic pleocytosis* | 6(21.4%) | 3(25%) | 3(18.8%) | 0.690 |
| *Elevated protein* | 9(25%) | 3(25%) | 6(37.5%) | 0.483 |
| MRI Changes | | | | |
| Normal MRI or residual changes | 15(28.6%) | 7(54.6%) | 8(20%) | 0.662 |
| Abnormal MRI (acute changes ≥ 2 cases) | 13(46.4%) | 5(45.5%) | 8(80%) | |
| FLAIR hHyperintensities with DWI restriction | | | | |
| *Medial temporal lobe* | 6(21.4%) | 4(33.3%) | 2(12.5%) | 0.184 |
| *Basal ganglia* | 4(14.3%) | 2(16.7%) | 2(12.5%) | 0.755 |
| *Multilobar* | 3(10.7%) | 1(8.3%) | 2(12.5%) | 0.724 |
| *Brainstem* | 5(17.9% | 1(8.3%) | 4(25%) | 0.255 |
| T2 shine through effect in bilateral PO region | 2(7.1%) | 1(8.3%) | 1(6.25%) | 0.832 |
| Intracranial bleed | 2(7.1%) | 1(8.3%) | 1(6.25%) | 0.832 |
| No of anaesthetic agents | | | | |
| <3 | 17(60.7%) | 7(58.3%) | 10(62.5%) | 0.823 |
| ≥3 | 11(39.3%) | 5(41.7%) | 6(37.5%) | |
| No of anaesthetic agent cyclings | | | | |
| <5 | 10(35.7% | 6(50%) | 4(25%) | |
| ≥5 | 18(64.3%) | 6(50%) | 12(75%) | 0.172 |
| Need for vasopressors | 25 (89.2%) | 12(42.8%) | 13(46.4%) | 0.112 |
| Mean delay in starting anaesthesia (hours) | 13.9±10.7 | 7.9±4.3 | 18.6±7.5 | <0.001 |
| Mean delay in starting IT in NORSE (days) | 6.8±3.1 | 4.1±0.9 | 9.8±2.4 | <0.001 |

ASIDs-after status epilepticus ictal discharges, BPDs-bilateral periodic discharges, BSP-burst suppression pattern, GPDs-generalised periodic discharges, IEDs-interictalepileptiform discharges, IT-immunotherapy, LPDs-lateralised periodic discharges, NCSE-non convulsive status epilepticus, NORSE-new onset refractory status epilepticus, PO-parieto occipital, SD-standard deviation, STESS-status epileptics severity score,

Patients were managed in our ICU mainly in concordance with SE guidelines (2012). Levetiracetam [n=23 (6.7%)] was the second most commonly used second-line drug after phenytoin Continuous intravenous anaesthetic agents were administered either combined or alone. The preferred first-line agent in use was midazolam (100%) followed by Thiopentone (57.1%) and ketamine (35.7%), Propofol (7.1%), and fentanyl (3.5%). All of the SRSE Patients received midazolam infusion which is the first choice in SRSE in our institute. IVMP (57.14%) and IVIG (50%), based on the consensus statement of the international encephalitis consortium 2012 were given for all patients with probable autoimmune encephalitis.

At discharge 8 patients (28.6%) died and 11 patients (39.3%) were in vegetative state. Out of the 28 patients, 12 patients (42.9%) had good outcome and 16 patients (57.1%) had bad outcome. Seven patients (25 %) were in vegetative state, five patients (17.9 %) need help in Activity of Daily Living and only four patients (14.3 %) need no assistance, are enlisted in Table 2

| GOS | At discharge | 1 year of follow up |
|---|---|---|
| Death | 8 (28.6%) | 9 (32.1%) |
| Vegetative state | 11(39.3%) | 7(25%) |
| Need help in all ADL | 4(14.3%) | 5(17.9%) |
| No need for help | 5(17.9%) | 4(14.3%) |
| Minimal Neuropsychological issues | 0 | 3(10.7%) |

Table 2; Outcome assessment using Glasgow outcome score at discharge and 1 year follow up.

Case fatality rate at the time of discharge was 28.6%, among these 6 (75%) had medical complications such as sepsis with multi organ dysfunction (MODS) [n=3 (50%)], Ventilator Associated Pneumonia (VAP) [n=2, 33.3%] and disseminated intravascular coagulation (DIC) [n=1, 17.7%].Anaesthetics induced hypotension was common and often required vasopressors during the hospital stay.

### 6.3 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 analyzed among SRSE patients at presentation was 2.3 + 1.1, score being significantly lower in patients with good outcomes versus bad (2.2+0.4 versus 2.8+0.8, p=0.025).

ii) Duration of ICU stay: The mean average duration of ICU stays in days was 65.7+22.9, significantly lower in patients with good outcomes versus bad outcomes (50.7+12.7 versus 78.3+15.8, p<0.001).

iii) Duration of ventilator support: The mean duration (days) of ventilator support was 43.9+16.8, lower in patients with good outcomes versus bad outcomes (38.7+8.3 versus 47.5+9.1, p=0.014).

iv)EEG findings: lateralised periodic discharges (LPDs) or earlier termed as periodic lateralised epileptiform discharges(PLEDs) [n=7(43.8%), p=0.040], non-convulsive status epilepticus (NCSE) in coma [n=9(56.3%), p=0.001], after status epilepticus ictal discharges (ASIDs) [n=9(56.3%), p=0.034], spontaneous burst-suppression pattern (sBSP) [n=11(68.8%), p=0.006] and post ictal diffuse attenuation of background activity [n=6(37.5%), p<0.001] were significantly associated with bad outcomes; whereas a post ictal return of normal background activity [n=5(41.7%), p=0.023] was significantly associated with good outcome.

v) Delay in starting anesthesia: The mean delay (hours) in starting anesthesia was 13.9+10.7, significantly lower in patients with good outcomes versus bad outcomes (7.9+4.3 versus 18.6+7.5, p<0.001).

vi)Delay in starting immunotherapy in NORSE: The mean delay (days) in starting immunotherapy in NORSE was 6.8+3.1, significantly lower in patients with good outcomes versus bad outcomes (4.1+0.9 versus 9.8+2.4, p<0.001).

Age, gender, prior comorbidities, etiology, semiology of SE, EEG findings other than the ones mentioned above, CSF or MRI, number of anaesthetic agents used and number of times they were recycled, Complications, and need of vasopressors were not significant predictors of outcome in SRSE.

Details of clinical, electrophysiological, radiological profiles and predictors of outcome in SRSE are enlisted in Table 1

**6.4. Predictors of outcome of SRSE by multivariate analysis**

The ones which were found significant by multivariate logistic regression analysis were (**Table 3**):

Duration of ICU stay (p<0.001), EEG findings such as NCSE in coma (0.032), sBSP (0.001) and post-ictal diffuse attenuation (<0.001), delay in starting anaesthesia (0.002) and delay in starting immunotherapy in NORSE (0.002) are found to be statistically influencing the outcome in patients with SRSE .

| **Table 3. Multivariate Logistic regression analysis for predictors of outcome in SRSE** | | | |
|---|---|---|---|
| **Variable** | **Adjusted odds ratio** | **95% C.I.** | **p Value** |
| **Duration of ICU stay** | 5.4 | 2.2–13.1 | <0.001 |
| **EEG** | | | |
| *NCSE in coma* | 1.8 | 1.1-2.9 | 0.032 |
| *sBSP* | 2.3 | 1.4–3.9 | 0.001 |
| *Post-ictal diffuse attenuation* | 4.1 | 1.9–8.7 | <0.001 |
| **Delay in starting anaesthesia** | 5.9 | 1.4–24.3 | 0.002 |
| **Delay in starting IT in NORSE due to AIE** | 4.3 | 2.6-21.3 | 0.015 |
| sBSP-spontaneous burst suppression pattern, AIE-Autoimmune encephalitis, IT-immunotherapy, NORSE-new onset refractory status epilepticus | | | |

Magnetic resonance imaging (MRI)-DTI was conducted in 14 patients with SRSE and 14 control participants. Brain areas were evaluated using diffusion maps, and fractional anisotropy (FA), mean diffusivity (MD), parallel diffusivity (λ||), and perpendicular diffusivity (λ⊥) values were extracted and analyzed. Tractography at the regions of abnormal diffusion indices was then reconstructed in each group. Compared to the control group, patients with SRSE had lower FA values and higher ADC values diffusely across all the white matter tract, Table;4 . Our data indicate that wide spread DTI abnormalities are associated with SRSE

## Table 4; DTI Data available for patients with SRSE and their controls

| | Case(n=14) | | Control (n=14) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| **ARF_FA_L** | 0.3495 | 0.0579 | 0.4309 | 0.0270 | -4.770 | 0.000 |
| **ARF_FA_R** | 0.3692 | 0.0594 | 0.4219 | 0.0334 | -2.896 | 0.008 |
| **ARF_ADC_L** | 0.8608 | 0.1542 | 0.7580 | 0.0415 | 2.408 | 0.023 |
| **ARF_ADC_R** | 0.8504 | 0.1514 | 0.7651 | 0.0586 | 1.966 | 0.060 |
| **CST_FA_L** | 0.4972 | 0.0578 | 0.5489 | 0.0326 | -2.917 | 0.007 |
| **CST_FA_R** | 0.4973 | 0.0696 | 0.5496 | 0.0458 | -2.345 | 0.027 |
| **CST_ADC_L** | 0.8664 | 0.0966 | 0.7455 | 0.0694 | 3.803 | 0.001 |
| **CST_ADC_R** | 0.8618 | 0.0825 | 0.7753 | 0.0652 | 3.079 | 0.005 |
| **ILF_FA_L** | 0.3835 | 0.0860 | 0.4599 | 0.0279 | -3.162 | 0.004 |
| **ILF_FA_R** | 0.4046 | 0.0656 | 0.4521 | 0.0404 | -2.305 | 0.029 |
| **ILF_ADC_L** | 0.9298 | 0.1669 | 0.7976 | 0.0343 | 2.902 | 0.007 |
| **ILF_ADC_R** | 0.8744 | 0.1373 | 0.7947 | 0.0748 | 1.907 | 0.068 |
| **IFOF_FA_L** | 0.3726 | 0.0506 | 0.4533 | 0.0185 | -5.609 | 0.000 |
| **IFOF_FA_R** | 0.3995 | 0.0643 | 0.4576 | 0.0392 | -2.884 | 0.008 |
| **IFOF_ADC_L** | 0.9092 | 0.1407 | 0.7962 | 0.0260 | 2.956 | 0.007 |
| **IFOF_ADC_R** | 0.8847 | 0.1376 | 0.8021 | 0.0685 | 2.011 | 0.055 |
| **SLF_FA_L** | 0.3112 | 0.0535 | 0.3691 | 0.0215 | -3.760 | 0.001 |
| **SLF_FA_R** | 0.3222 | 0.0549 | 0.3756 | 0.0251 | -3.312 | 0.003 |
| **SLF_ADC_L** | 0.9413 | 0.1864 | 0.8146 | 0.0501 | 2.457 | 0.021 |
| **SLF_ADC_R** | 0.9230 | 0.2028 | 0.8201 | 0.0550 | 1.832 | 0.078 |
| **UF_FA_L** | 0.3174 | 0.0518 | 0.3792 | 0.0197 | -4.175 | 0.000 |
| **UF_FA_R** | 0.3205 | 0.0467 | 0.3917 | 0.0174 | -5.344 | 0.000 |
| **UF_ADC_L** | 0.9652 | 0.1601 | 0.8417 | 0.0327 | 2.830 | 0.009 |
| **UF_ADC_R** | 0.9182 | 0.1249 | 0.8070 | 0.0344 | 3.210 | 0.004 |

Table 4 ; DTI data of 14 available patients with matched age and sex controls ; FA – Fractional Anisotropy, ADC – Absolute diffusion coefficient UF- Uncinate Fasciculus, ARF –Arcuate Fasciculus, ILF – Inferior Longitudinal Fasciculus SLF – Superior Longitudinal Fasciculus , CST – Cortical Spinal Tract

EMR records analysed during one year follow up also showed seizure recurrences in 42.8% of all individuals with 25 % patients had focal onset seizures with impaired awareness and two patients had status epilepsy .None of the patients had a second super refractory status epilepsy event on follow up. (Figure 2)

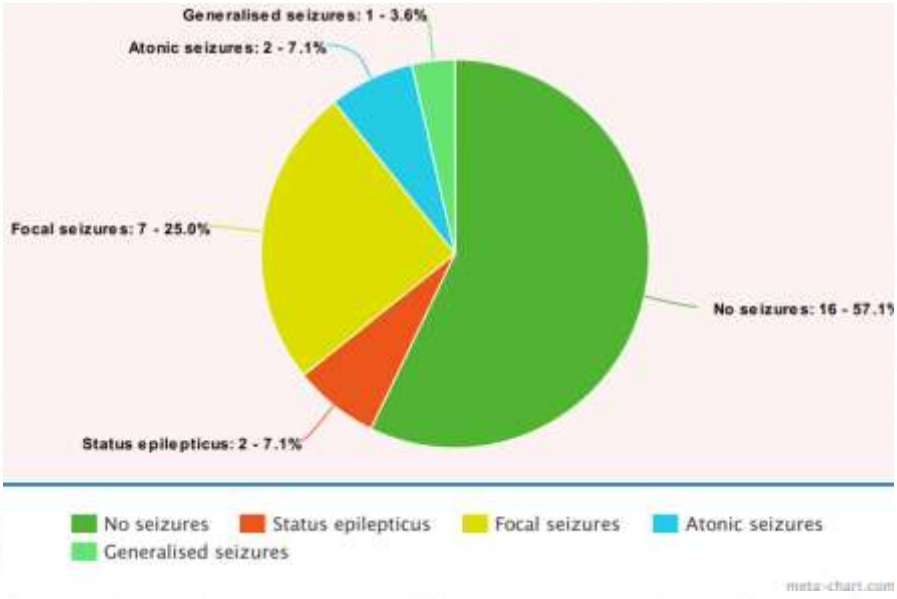



Figure 2; Seizure status at follow up

# DISCUSSION

## 7. DISCUSSION

SRSE, though a rarer entity is a dreaded emergency with high morbidity and mortality even in developed countries. Intensive monitoring should be meticulously planned from the beginning of admission itself. Our study planned to identify factors predicting the outcome such that from the initial presentation itself, we can prognosticate and direct the management accordingly.

The prevalence of Super Refractory Status Epilepsy was 8% which is in concordance with many published data previously (40).A homogenous protocol-driven approach with continuous EEG monitoring and strict vigilance on medical complications has resulted in mortality of about 28% which is lower compared to the mortality of 36-40%. The study comprises a majority of the younger population with a mean average of 18 years. Thus SRSE may be a disease of the younger population and can occur de novo as the majority neither had any previous seizures, any structural changes, or positive family history. The acute symptomatic entity was the most common etiology followed by cryptogenic, remote symptomatic, and progressive symptomatic. However when analyzed etiologies had no impact on the outcome.

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 [41]. NORSE and FIRES as entities are recently being recognized, and in our study18 patients were NORSE category among which 5 patients were FIRES. The majority of patients received immunotherapy keeping in view that encephalitis is a major contributor to the initiation of SRSE. There is also evidence that delay in initiating immunotherapy will adversely affect the outcome.

Midazolam was the preferred anaesthetic agent and has been our preference which was published (43), followed by Thiopentone, ketamine, and Propofol. In RSE and SRSE, burst suppression provides an arbitrary target for the titration of anaesthetic treatment with the drug dosing commonly set in a way in which burst suppression is aimed at inter burst intervals of 2–30 s or an isoelectric EEG pattern. Spontaneous burst suppression was obtained in a quarterly of patients and had an association with bad outcomes. SRSE can lead to irreversible neurological network changes which were exemplified in our study with spontaneous burst suppression and diffuse attenuation pattern which was more with a bad outcome.

Prolonged periods of burst suppression with anesthetics are directly related to mortality mainly due to its cardiac depressant effects (42). Continuous EEG monitoring helps in identifying electrographic seizures, titrate anaesthetic agents and anti-epileptic drugs, monitoring burst suppression patterns.

SRSE develops due to acute insult within the neuronal network and it triggers and propagates further seizures and NCSE in a coma was a predictor for bad outcomes. Sepsis and Ventilator-Associated Pneumonia were the common complications noted in our study. Anaesthesia-induced complications like hypotension and cardiac arrhythmia are due to the direct cardiac depressant effects of the anesthetics.

Prolonged duration of hospital ICU stay, increases medical complications and can affect mortality. ICU complications were responsible for about 75 % of mortality despite the good control of SE. Hence it is imperative to taper anesthesia and wean off the patient from the ventilator early once SRSE is controlled, to reduce the duration of ICU stay and prevent major complications to ensure better outcomes.

“Time is brain” in SE management conveys the need for starting anesthetics without much delay. ILAE task force recommends SE to be controlled very early before irreversible injury sets in, within the time-frames t1 (5 minutes) and t2 (30 minutes). Delay in treatment particularly about anesthetics, ventilator care, and cEEG monitoring is a dream ahead for many developing nations in managing SRSE patients and it was very evident from our study and this issue is to be addressed. Many times such patients are managed with limited options like multiple ASMs alone or ASMs along with low-dose continuous intravenous benzodiazepines or barbiturate infusion for saving the patient [43]. C EEG alone

will help detect NCSE and recurrent NCSE in SRSE is a marker of a bad outcome as it causes cerebral hypoxia on account of recurrent seizures, and also begets evolution from RSE to SRSE by internalization of GABAA postsynaptic receptors and increase in excitatory N-methyl-D-aspartate receptors over time [42].

Our study also addressed the total number of anesthetics and the number of cyclings of anesthetics, whether it affects the outcome as anesthetics form an important and first-line agent in managing an established SRSE. Even after reaching maximum tolerated doses of an anesthetic, one can try using it again after the next available anesthetic agent(s) fail, starting another cycle all over again till one can break the chain of ongoing seizures which is defined as "recycling of anaesthetic agents". We found that neither the increased number of anaesthetic agents used nor the repeated recycling of any of these drugs singly or in combination caused a bad outcome. (Table 3). Though SRSE is a disease with significant morbidity, it is not advisable to stop the quality care as about 1/3 rd of patients can have good outcomes even after weeks and months which was described earlier also [2]. Nevertheless, once the anaesthetic agents have be stopped

accomplished the endpoint of the abolition of seizures as seen in cEEG, it should as anaesthetic complications like cardiac suppression are frequent and can be life-threatening.

MRI findings did not have any impact on the outcome of SRSE patients. DTI studies done separately with 14 available SRSE patients and 14 age-sex match controls suggest diffuse tract involvement in such patients (Table 4). A physiological and molecular level insult triggers the seizures and it alters the neuronal circuit which further propagates the seizures as exemplified by t1 and t2 time frames and hence specific treatment should be started early [41].

Through this study, it was evident the difficulties faced in developed countries particularly about the treatment delay of SRSE, delay in starting immunotherapy, and obviously, the hospital burden with longer duration of ICU stay. Our study helps in understanding better the etiology and predictors of outcome in SRSE as there is a huge gap in understanding the disease entity as such with the absence of randomized controlled and multi-centric trials.

# LIMITATIONS

## 8. LIMITATIONS

Exact details of time spend in SE and delay before 1sst line and second-line agents were not available since the majority of our patients were treated initially from outside and are referred from other secondary level hospitals. SRSE is a disease of rarity and our study cohort only comprises 28 patients, however, it was better than many studies which have taken SRSE alone for analysis. Though the total study duration was about 20 years we did not separately study the outcome and year of admission. Newer drugs such as Lacosamide, Perampanel and their impact on controlling the maintenance phase of SE and its prognosis need to be ascertained in future follow-up studies. EEG parameters such as loss of posterior dominant rhythm and sleep architecture were not studied in the present study.

# CONCLUSION

## 9. CONCLUSION

The study was able to predict the independent therapeutic and electrophysiological prognostic factors for SRSE. A meticulous uniform protocol approach should be in the forefront while dealing with SRSE and it will result in improved outcomes in about 1/3rd of patients. Despite the prolonged duration of status for many weeks or even months, the outcome is not bad as expected. Auto-immune encephalitis is increasingly being diagnosed to be associated with SRSE and has to manage aggressively. cEEG monitoring is mandatory in comatose patients with SRSE even after optimal management and NCSE needs to be addressed from the beginning itself. Strict vigilance on preventing medical complications should be there while managing patients. Recurrent NCSE and delay in hospital admission, delay in starting anesthesia, and immunotherapy are associated with a bad outcome. The time-tested aphorism "time is brain" is true for SE in general and the adage for SRSE is brain needs time to recover.

# REFERENCES

## 10. REFERENCES

[1] Hocker S, Wijdicks EF, Rabinstein AA. Refractory status epilepticus: new insights in presentation, treatment, and outcome. Neurol Res. 2013; 35(2):163– 8.

[2] Ferlisi M, Shorvon S. The outcome of therapies in refractory and super- refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135(Pt. 8):2314–28.

[3] Holtkamp M, Othman J, Buchheim K, Masuhr F, Schielke E, Meierkord H. A malignant variant of status epilepticus. Arch Neurol. 2005; 62(9)1428–31.

[4] Kilbride RD, Reynolds AS, Szaflarski JP, Hirsch LJ. Clinical outcomes following prolonged refractory status epilepticus (PRSE). Neurocrit Care. 2013; 18(3):374–85.

[5] Lai A, Outin HD, Jabot J, Megarbane B, Gaudry S, Coudroy R, et al. Functional outcome of prolonged refractory status epilepticus. Crit Care. 2015; 19(1):199

[6] Sutter R, Kaplan PW,Marsch S,Hammel EM,Rüegg S,Ziai WC. Early predictors of refractory status epilepticus:aninternational two-center study.Eur J Neurol (2015)22(1):79–85.

[7] . Giovannini G,Monti G,Polisi MM,Mirandola L, Marudi A,Pinelli G,et al.A one-year prospective study of refractory status epilepticus in Modena,Italy.Epilepsy Behav(2015)49:141–5.

[8] ZelanoJ,Möller F,Dobesberger J,TrinkaE,Kumlien E.Infections in status epilepticus:a retrospective 5-yearcohort study.Seizure(2014)23(8):603–6.

[9] Misra UK,Kalita J,Nair PP.Status epilepticus in central ner vous system infections: an experience from a developing country.Am J Med (2008)121(7):618–23.

[10] Eugen Trinka, Hannah Cock, Dale Hesdorffer, Andrea O. Rossetti, Ingrid E. Scheffer, Shlomo Shinnar, Simon Shorvon, and Daniel H. Lowenstein . A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus Epilepsia, 56(10):1515–1523, 2015

[11] China Yaohua Li, Linyu Tian, Tianfang Zeng, Jiani Chen, Lei Chen, Dong Zhou . Clinical features and outcome of super-refractory status epilepticus :A retrospective analysis in West Department of

Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China. Seizure 23 (2014 ) 222- 227

[12] Alexandre Lai, Hervé D Outin, Julien Jabot, Bruno Mégarbane, Stéphane Gaudry, Rémi Coudroy, Guillaume Louis, Francis Schneider, Nicolas Barbarot, Antoine Roch, Nicolas Lerolle, David Luis, François Fourrier, Anne Renault, Laurent Argaud, Tarek Sharshar, Sébastien Gibot, and Pierre-Edouard Bollaert. Functional outcome of prolonged refractory status epilepticus. Crit care 2015; 19(1): 199.

[13] Jayalakshmi S, Ruikar D, Vooturi S, Alladi S, Sahu S, Kaul S, et al. Determinants and predictors of outcome in super refractory status epilepticus – a developing country perspective. Epilepsy Res (2014) 108:1609–17

[14] Kohli S, Pasangulapati SB, Yoganathan S, Rynjah GL, Prabhakar AT, Aaron S, et al. Study of refractory status epilepticus from a tertiary care center. Ann Indian Acad Neurol (2017) 20:116–21.

[15] Strzelczyk A, Ansorge S, Hapfelmeier J, Bonthapally V, Erder MH, Rosenow F. Costs, length of stay, and mortality of super-refractory status epilepticus: a population-based study from Germany. Epilepsia (2017) 58(9):1533–41.

[16] Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates: ischemic cell change and its relation to ictal physiological events. Arch Neurol 1973; 28: 10–7

[17] Kantanen AM, Reinikainen M, Parviainen I, Ruokonen E, Ala-Peijari M, Bäcklund T, et al. Incidence and mortality of super-refractory status epilepticus in adults. Epilepsy Behav. 2015; 49:131-4.

[18] Fountain NB, Lothman EW. Pathophysiology of status epilepticus. J Clin Neurophysiol. 1995;12(4):326–42.

[19] Fujikawa DG. The temporal evolution of neuronal damage from pilocarpine-induced status epilepticus. Brain Res. 1996;725:11–22.

[20] Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. J Neurosci. 1997;17:7532–4

[21] Mazarati AM, Wasterlain CG, Sankar R, Shin D. Self-sustaining status epilepticus after brief electrical stimulation of the perforant path. Brain Res. 1998;801:251–3

[22] Mazarati AM, Baldwin RA, Sankar R, Wasterlain CG. Time dependent decrease in the effectiveness of antiepileptic drugs during

the course of self-sustaining status epilepticus. Brain Res. 1998;814:179–85.

[23] Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus: Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998;339:792–8

[24] Mazarati AM, Wasterlain CG. N-Methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. Neurosci Lett. 1999;265:187–9

[25] Arancibia-Carcamo IL, Kittler JT. Regulation of GABAA receptor membrane trafficking and synaptic localization. Pharmacol Ther. 2009;123:17–31.

[26] Smith KR, Kittler JT. The cell biology of synaptic inhibition in health and disease. Curr Opin Neurobiol. 2010;20:550–6.

[27] Naylor DE, Liu H, Niquet J, Wasterlain CG. Rapid surface accumulation of NMDA receptors increases glutamatergic excitation during status epilepticus. Neurobiol Dis. 2013;54:225–38.

[28] Cock HR, Tong X, Hargreaves I, Heales SJR, Clark JP, Patsalos PN, et al. Mitochondrial dysfunction associated with neuronal death following status epilepticus in rat. Epilepsy Res. 2002;48:157–68.

[29] Tan RY, Neligan A, Shorvon SD. The uncommon causes of status epilepticus: a systematic review. Epilepsy Res. 2010;91:111–22.

[30] Marchi N, Granata T, Freri E, Ciusani E, Ragona F, Puvenna V, et al. Efficacy of anti-inflammatory therapy in a model of acute seizures and in a population of pediatric drug resistant epileptics. PLoS One. 2011;28:e18200.

[31] David Y, Cacheaux LP, Ivens S, Lapilover E, Heinemann U, Kaufer D, et al. Astrocytic dysfunction in epileptogenesis: consequence of altered potassium and glutamate homeostasis? J Neurosci. 2009;29:10588–99.

[32] Friedman A, Dingledine R. Molecular cascades that mediate the influence of inflammation on epilepsy. Epilepsia. 2011;52 Suppl 3:33–9.

[33] Henshall DC. MicroRNAs in the pathophysiology and treatment of status epilepticus. Front Mol Neurosci. 2013;6:37.

[34] Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. J Neurol. 2008; 255(10):1561–6

[35] Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975; 1(7905):480-4.

[36] Gaspard N, Hirsch LJ, Sculier C, Loddenkemper T, van Baalen A, Lancrenon J, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): State of the art and perspectives. Epilepsia. 2018; 59(4):745-752.

[37] Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M; Neurointensive Care Section of the European Society of Intensive Care Medicine. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med. 2013; 39(8):1337-51.

[38] Herman S, Abend N, Bleck T, Chapman KE, Drislane FW, Emerson RG, et al. Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I. Journal of Clinical Neurophysiology. 2015;32(2):87-95.

[39] Kate MP, Dash GK, Radhakrishnan A. Long-term outcome and prognosis of patients with emergent periodic lateralized epileptiform discharges (ePLEDs). Seizure. 2012; 21(6):450-6.

[40] Madžar D, Knappe RU, Reindl C, Giede-Jeppe A, Sprügel MI, Beuscher V, et al. Factors associated with occurrence and outcome of super-refractory status epilepticus. Seizure. 2017; 52:53-59.

[41]. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015; 56(10):1515-23.

[42]. Niquet J, Baldwin R, Suchomelova L, Lumley L, Naylor D, Eavey R, et al. Benzodiazepine-refractory status epilepticus: pathophysiology and principles of treatment. Ann N Y Acad Sci. 2016; 1378(1):166-173

# ANNEXURES

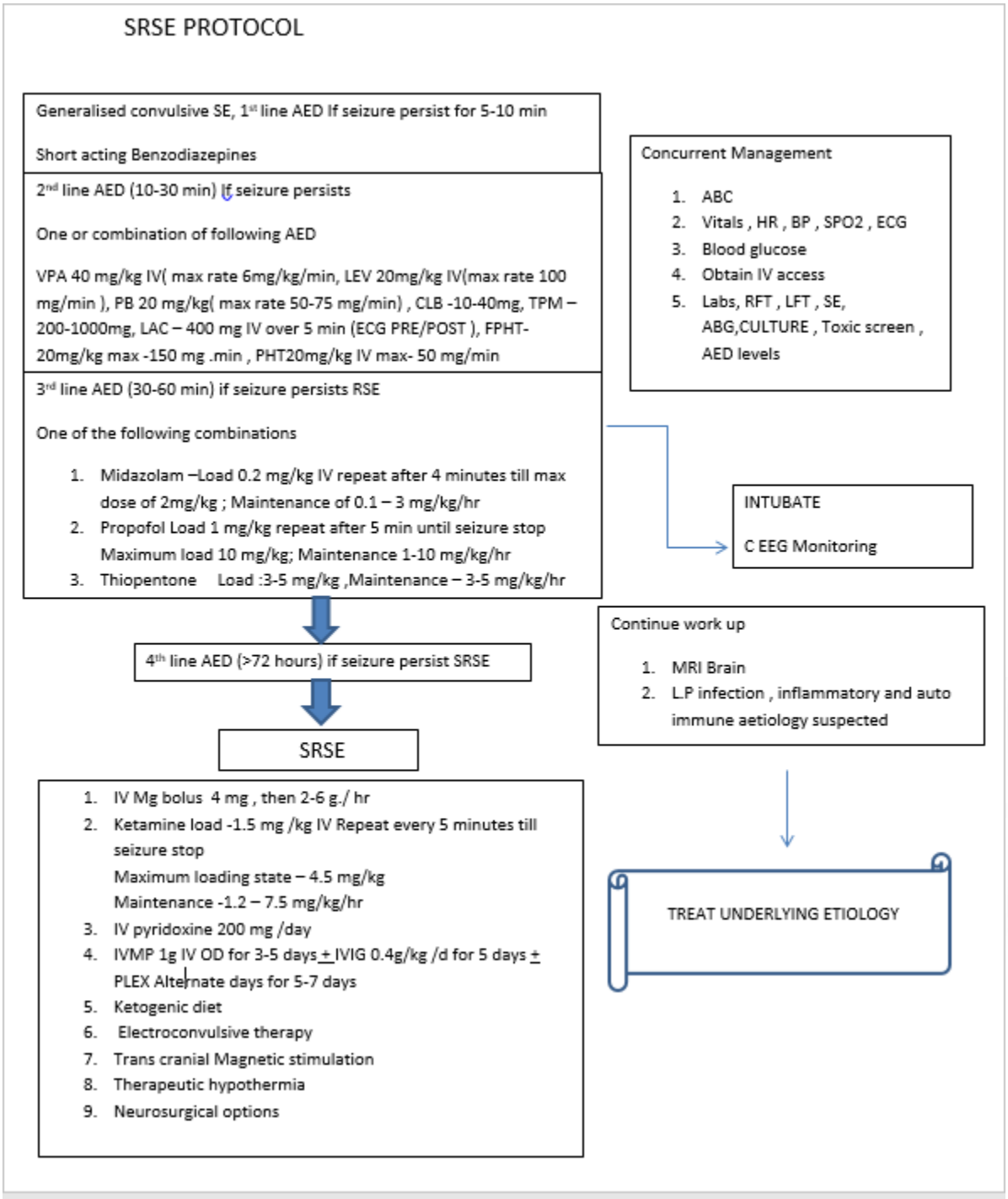
## 1. STESS SCORE

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

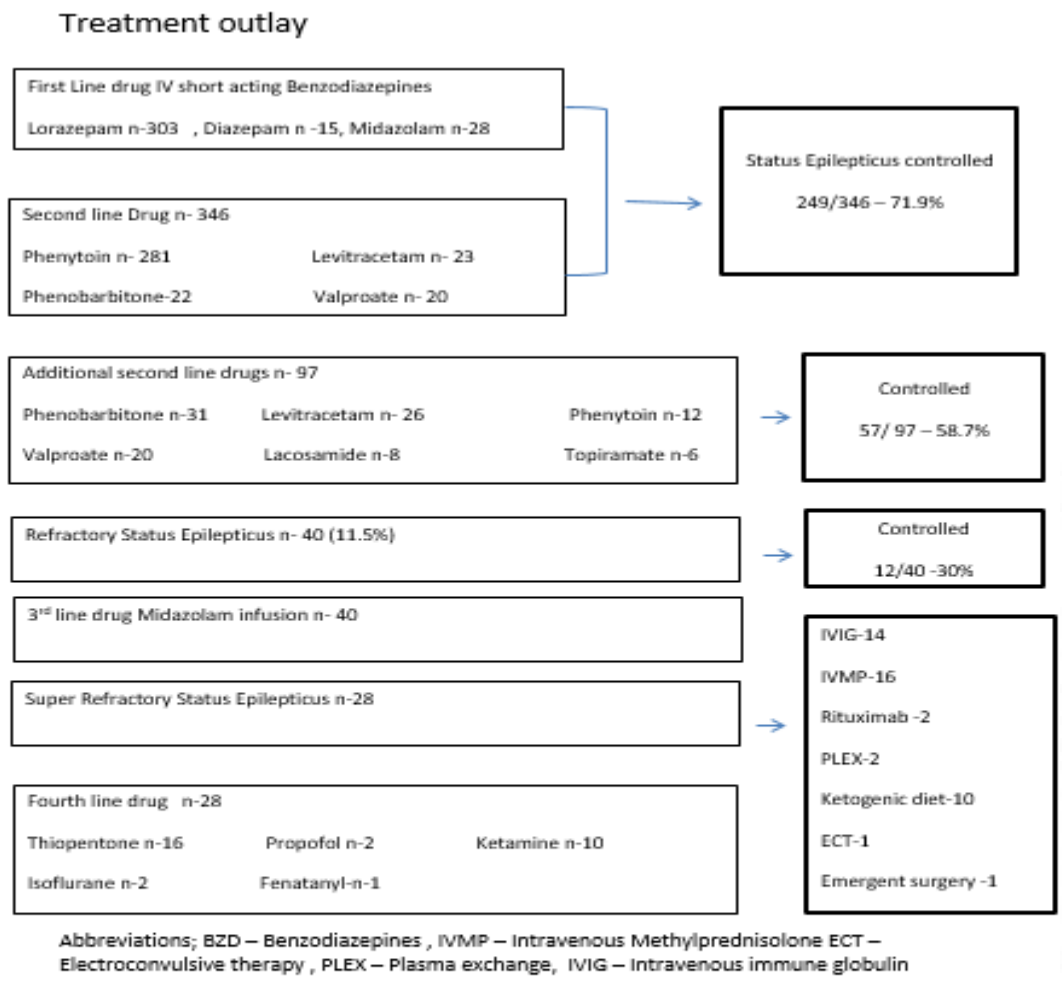
## 3. SRSE PROTOCOL



## 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<br>% of RSE /SRSE | Outcome | comments |
|---|---|---|---|
| Hassan et al , 10 years , 1 , india | N-84<br>21 % RSE , 7%SRSE | Seizures controlled in in 69.6% of RSE<br>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<br>40.7% RSE<br>16.7% SRSE | 40% Mortality and 33.3% good outcome in SRSE<br>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<br>13% SRSE | 43 % Mortality in SRSE | SRSE Patients with treatable aetiology has better outcome |
| Giovannini etal , 1 year , 1 Italy | N- 83<br>14% RSE<br>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<br>78% RSE<br>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<br>33.3% RSE<br>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<br>20.4% RSE<br>12.2% SRSE | 50% Mortality in SRSE | 67% SRSE due to viral encephalitis and <10% had prexisting epilepsy |

## 5. Treatment Outlay




Abbreviations; BZD – Benzodiazepines , IVMP – Intravenous Methylprednisolone ECT – Electroconvulsive therapy , PLEX – Plasma exchange, IVIG – Intravenous immune globulin

**ABBREVIATIONS**

**ILAE – International League Against Epilepsy**

**NORSE- New Onset Refractory Status Epilepticus**

**FIRES – Febrile Infection Related Epilepsy Syndrome**

**SRSE –Super Refractory Status Epilepticus**

**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**

## PROFORMA

## Study variables

(Retrospectively collected from discharge summaries and case records)

## AT ADMISSION

Age of the patient

Sex

Male -1

Female -2

**Past history of illness**

Trauma

Surgery

Stroke

Seizures

Toxins

Family history of seizures

Yes -1

NO -2

Presenting complaints

Fever

Headache

Vomiting

Seizures

Rash

Altered sensorium

Focal deficits

Types of seizures

Focal with awareness-1

Focal without awareness-2

Generalised-3

NORSE -1, FIRES -2

NCSE 1 – Yes 2 – Nil

STESS Score at admission

MRS Score at presentation

CSF

Pleocytosis -1

Hypoglycorrhacia -2

Elevated protein-3

OCB Positive -4

Elevated IG G index-5

Auto immune panel

GAD-1

NMDA-2

VGKC -3

GABA-4

AMPA - 5

EEG

Type of seizures 1- focal, 2- Generalised

IED –1. Focal, 2.multifocal, 3. Generalised

PLED Present -1, not present -2

ASID – present 1 , not present -2

Burst suppression achieved – 1, Not achieved-2

NCSE at presentation Yes -1 No -2

MRI -Structural changes

Acute phase

1. normal , 2. Temporal lobe abnormal , 3 . Insular changes , 4. cortical edema , 5. cerebellar edema or haemorrhage, 6. thalamus abnormal signal , 7. Basal ganglia changes, 8. brain stem changes , 9 . Multifocal sub cortical infarcts, 10. vascular malformations

chronic phase –

1. Normal, 2. Gliosis , 3. Encephalomalacia, 4. MTS , 5.Basal ganglia changes, 6. Thalamic changes , 7. ependymal enhancement, 8. insular changes, 9. abnormal white matter changes , 10. abnormal signal in tracts

Functional parameters

DTI

1. FA value
2. ADC
3. Tract volume

Complications

1. UTI, 2. Pneumonia, 3. Electrolyte disturbance, 4. Thrombotic complications 5. Cardiac complications

AED used

1. 1st line agents
2. 2nd line agents
3. IV Anaesthetics

Duration of ICU Stay-

## AT DISCHARGE

GOS Score at discharge

## FOLLOW UP LATER AT 1 YEAR

(Retrospectively collected from EMR documents)

Seizure status at follow up
1-remission
2-Recurrence
Seizure type – 1. Focal, 2.generalised, 3. Status epilepsy

GOS score

**IEC APPROVAL LETTER**

## Institutional Ethics Committee

**(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)**

SCT/IEC/ 1441/OCTOBER-2019 21.11.2019

**Dr. Jithu Jose**
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Jithu Jose,

The Institutional Ethics Committee reviewed your application to conduct the study entitled "CLINICO-ELECTRO-RADIOLOGICAL PREDICTORS OF OUTCOME IN SUPER REFRACTORY STATUS EPILEPTICUS (IEC/1441)" on 21st November, 2019.

**The following documents were reviewed:**

*Original submission*

1. *Covering Letter addressed to the Chairman, IEC, SCTIMST with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *CV of Principal Investigator and Co-Principal Investigator*

*Revised submission*

1. *Covering Letter addressed to the Chairperson,* [illegible] *cklist*
2. *TAC Approval Letter*
3. *IEC Applicatio* 47 *ject Proposal*
5. *Proforma*
6. *CV of Principal* [illegible] *ncipal Investigator*

**The IEC Review Criteria**

The study fulfils the expedited criteria from [illegible] a vide section 9.1 of the Standard Operating Procedures (April 2017) of the SCTIMST-IE

**IEC Decision**

The IEC approved the conduct of the study in the present form.

***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,*

**Mala Ramanathan**
*Member Secretary, IEC*

Check Plagiarism

Don't Worry! This report is 100% safe & secure. It's not available publically and it's not accessible by search engines (Google, Yahoo. Bing, etc)

| | |
|---|---|
| **Report Title:** | srse |
| **Report Link:** (Use this link to send report to anyone) | https://www.check-plagiarism.com/plag-report/363207eb58278088d53ff358579bf6a51cf351626801393 |
| **Report Generated Date:** | 20 July, 2021 |
| **Total Words:** | 2635 |
| **Total Characters:** | 16595 |
| **Keywords/Total Words Ratio:** | 0% |
| **Excluded URL:** | No |
| **Unique:** | 92% |
| **Matched:** | 8% |

## Match Urls:

0: https://en.wikipedia.org/wiki/Receptor

1: https://www.merriam-webster.com/dictionary/activity

2: https://www.mielecarehome.co.uk/assets/downloads/files/Infection_Control_Implementation_Plan_out.pdf

3: https://en.wiktionary.org/wiki/se

4: https://www.merriam-webster.com/dictionary/unwanted

5: http://www.60plus.se/

6: https://www.sciencedirect.com/topics/neuroscience/tractography

7: https://pubs.rsna.org/doi/pdf/10.1148/radiol.2016152832

8: https://www.thefreedictionary.com/4

9: https://www.spandidos-publications.com/10.3892/mmr.2017.8277

10: https://www.flapinhibitor.com/2017/04/19/a-p-value-of-less-than-0-05-was-considered-statistically-significant/

11: https://www.jianshu.com/p/551a62600f46

12: https://malesbecomefemales.blogspot.com/search/label/Marrying%20Friend

13: https://politiken.e-pages.dk/?mode=kc&issue=20210706&sub=59077c46-5b24-4c0d-a49c-9d05d1dc4825&key=679c385a3cba539f6b4f33d38a48f71d&sig=unknown+0.0.0&page=1

14: https://samplepapers.us/give-an-example-of-a-good-decision-that-you-made-that-resulted-in-a-bad-outcome/

15: https://ceribell.com/clinical_condition/non-convulsive-status-epilepticus-ncse/

16: https://en.wikipedia.org/wiki/Laguz

17: https://www.ncbi.nlm.nih.gov/pubmed/25246354

18: https://www.sid.ir/FileServer/JE/86820180406.pdf