CARDIAC ABNORMALITIES IN REFRACTORY STATUS EPILEPTICUS- A PROSPECTIVE OBSERVATIONAL STUDY

THESIS SUBMITTED TO

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

In partial fulfilment of the requirement for the degree of

DOCTORATE OF MEDICINE (D.M)

(NEUROLOGY)

JULY 2020 **DR. DEEPIKA SAROHA**

AIIMS, JODHPUR

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

DECLARATION

I hereby declare that the thesis titled **"CARDIAC ABNORMALITIES IN REFRACTORY STATUS EPILEPTICUS - A PROSPECTIVE OBSERVATIONAL STUDY"** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

Dr. Deepika Saroha
Department of Neurology
All India Institute of Medical Sciences, Jodhpur

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

CERTIFICATE

This is to certify that the work embodied in the thesis entitled **"CARDIAC ABNORMALITIES IN REFRACTORY STATUS EPILEPTICUS - A PROSPECTIVE OBSERVATIONAL STUDY"** has been conducted by Dr. Deepika Saroha under our supervision and guidance in the Department of Neurology, All India Institute of Medical Sciences, Jodhpur, Rajasthan. The results and observations of this study have been checked and verified by us from time to time. The thesis contains the candidate's own genuine and independent work.

SUPERVISOR

DR. SAMHITA PANDA
Additional Professor and Head, Department of Neurology
All India Institute of Medical Sciences, Jodhpur

CO-SUPERVISORS

DR. SURENDER DEORA Additional Professor, Department of Cardiology All India Institute of Medical Sciences, Jodhpur	
DR. SADIK MOHAMMED Additional Professor, Department of Anesthesiology and Critical Care All India Institute of Medical Sciences, Jodhpur	

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

CERTIFICATE

This is to certify that the thesis titled **"CARDIAC ABNORMALITIES IN REFRACTORY STATUS EPILEPTICUS - A PROSPECTIVE OBSERVATIONAL STUDY"** is the bonafide work of Dr. Deepika Saroha carried out under guidance and supervision, in the Department of Neurology, All India Institute of Medical Sciences, Jodhpur, Rajasthan.

GUIDE

Dr. Samhita Panda
Additional Professor and Head
Department of Neurology
All India Institute of Medical Sciences, Jodhpur

ACKNOWLEDGEMENT

It is my privilege to have had an esteemed guide in ***Dr. Samhita Panda****, Additional Professor and Head, Department of Neurology,* who has been my mentor for 3 years. She has provided her valuable guidance and help without fail during every step of this study. Her constant encouragement, scientific temper, knowledge and expertise for the subject enabled me to present this thesis. Her benefaction and patronage allowed me to view things with the right perspective.

I am deeply indebted to my co-guide ***Dr Surender Deora****, Additional Professor, Department of Cardiology,* ***Dr Sadik Mohammed****, Additional Professor, Department of Anesthesiology and Critical Care* for the generous help, constant support and continuous guidance which they bestowed upon me from time to time throughout the course of completion of this thesis and always been a source of inspiration.

My special mention of thanks to ***Dr. Sarbesh Tiwari****, Associate Professor, Department of Diagnostic and Interventional Radiology,* for enriching me with the knowledge of radiology and for being a source of inspiration for his unmatchable enthusiasm of teaching and excellence in academics.

My heartfelt gratitude to my reverent teachers, ***Dr. Deepak Jha*** *(Professor and Head, Department of Neurosurgery)****, Dr. Suryanarayanan Bhaskar*** *(Professor, Department of Neurosurgery)****, Dr. Mayank Garg*** *(Additional Professor, Department of Neurosurgery)* for the knowledge they imparted to me. I am indebted for their generous guidance.

I am immensely thankful to ***Dr. Sucharita Anand, Dr. Anka Arora*** *and* ***Dr. Sanjiv Sharma, Dr Saksham Jain, Dr. Apoorv Patel, Dr Monalisa Vegda*** for teaching me the clinical and practical aspects of neurology and for always being supportive in my pursuits.

A special mention of thanks to my Juniors ***Dr. Krishnakanth Ravi, Dr. Naman Aggrawal, Dr. Khetaram Sharma, Dr Hemant Luniwal, Dr Rahul Naik and Dr Rohit Kushwah*** for their constant support and cooperation during this entire journey. Their timely help shall always be remembered.

I am eternally thankful to my parents, ***Mr. Ashok Kumar Saroha*** and ***Mrs. Anita***

Saroha and my brother, ***Mr. Deepak Saroha*** for providing unfailing support and continuous encouragement throughout my study. This accomplishment would not have been possible without their patience, perseverance and continuous motivation throughout the years. My lovely husband ***Mr. Pranat Kumar Joshi*** who always pacifies me and has provided emotional and mental support and for that any amount of thanks is inadequate.

Our experienced electrophysiology staff, ***Mr Arman Gahzi, Mr Praveen Kachwaha*** and ***Mr Praveen Rao*** who were always on their feet to help in all technical aspects.

And lastly, to all my patients, without whom, I am no doctor, and a little less empath.

Dr. Deepika Saroha

ABBREVIATIONS

ASM	Anti Seizure Medication
ILAE	International League Against Epilepsy
ECG	Electrocardiogram
2D Echo	2 Dimensional Echocardiogram
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
mRS	Modified Rankin Scale
SE	Status Epilepticus
RSE	Refractory Status Epilepticus
SRSE	Super Refractory Status Epilepticus
NORSE	New Onset Refractory Status Epilepticus
FIRES	Febrile Infection Related Epilepsy
NCSE	Non Convulsive Status Epilepticus
CSE	Convulsive Status Epilepticus
HR	Heart Rate
HRV	Heart Rate Variability
AF	Atrial Fibrillation
AFL	Atrial Flutter
VF	Ventricular Fibrillation
VFL	Ventricular Flutter
A V Block	Atrial ventricular block
Trop I	Troponin I
NT pro BNP	N-Terminal pro b-type natriuretic peptide
QTc	Corrected QT interval
NICU	Neurology Intensive Care Unit
ICU	Intensive Care Unit
IV	Intravenous
MV	Mechanical Ventilation

ER	Emergency Room
PLEDS	Periodic Lateralized Epileptiform Discharges
SDNN	Standard Deviation of Inter Beat Interval Of Normal Sinus Beats
RMSSD	Root Mean Square of Successive Differences Between Normal Heartbeats
i.e.	That is
e.g.	For example
RWMAs	Regional Wall Motion Abnormalities
STESS	Status Epilepticus Severity Score

CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY

Background: Cardiac abnormalities have been reported during seizures and recently in RSE. ECG, Holter, 2D Echo, Trop I, and NT pro BNP are non-invasive, tools used to evaluate these cardiac abnormalities. Recently, reduced heart rate variability (HRV) and cardiac arrhythmias have been proposed as factors for sudden unexpected death in epilepsy.

Objective: To assess markers of cardiac injury, ECG and 2D Echo changes in patients with RSE and to correlate these cardiac abnormalities within 24-hours of RSE with prognosis and functional outcome of patients at discharge/death and at short term follow up of 30-days.

Methods: A total of 20 patients of RSE underwent ECG, Holter, Trop I, NT Pro BNP, and 2D Echo analysis. Using ECG and holter evaluation, heart rate changes /arrhythmias, QTc and HRV were studied, while ventricular dysfunction or regional motion wall abnormality (RWMA) were studied on 2D Echo. NT Pro BNP and Trop I was done for all patients. These parameters were first studied during hospital stay, discharge or death and 30 days post discharge.

Results: This prospective observational cohort study was conducted over 18 months. Total of 20 patients with RSE, fulfilling the inclusion criteria were recruited after due informed consent from their attendants. Mean age was 47.75±17.2 years with male: female ratio of 1:1. Mean time interval between onset of seizure and presentation to ER was 8.80+/-7.024 hours. CNS infection (35%) followed by autoimmune encephalitis (20%) and cerebrovascular disease (20%) were the most common etiologies. Cardiac injury markers including QTc prolongation, raised Trop I and NT pro BNP, ST changes, LV and/or RV dysfunction and RWMA were studied. Out of these cardiac injury markers, cardiac enzymes and QTc prolongation were the commonest cardiac abnormalities in RSE. Both reduced HRV and presence of cardiac injury markers, which had significant correlation with poor outcome in our study, can be used as a prognostic marker. Apart from these, poor GCS and mRS at presentation, and presence of NCSE were

also found to be associated with poor outcome.

Conclusion: Markers of cardiac injury and reduced HRV in addition to poor GCS, poor mRS and occurrence of NCSE have a consistent correlation with mortality and poor clinical outcome. Routine analysis of ECG, 2D Echo, holter and cardiac enzymes like NT –Pro BNP and Trop I as affordable, easily accessible, and non-invasive tools to assess cardiac abnormalities in RSE patients is recommended.

INTRODUCTION

Status Epilepticus (SE) is defined clinically or electrographically by the presence of continuous seizure activity at least 5 min in duration or recurrent seizure activity without recovery between seizures. ILAE 2015 proposed a new definition of SE as a condition resulting either from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms, which cause abnormally, prolonged seizures (after time point t1). SE can result in long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures. In the case of convulsive (tonic–clonic) SE, t1 is 5 mins and t2 is 30 mins). There is limited information available to define t1 and t2 in focal SE, and no information is available at present for absence SE. Refractory Status Epilepticus (RSE) is defined as SE persisting despite sufficient dose of benzodiazepines and at least one antiseizure medication (ASMs), irrespective of time. Super Refractory Status Epilepticus (SRSE) is defined as SE that continues for 24 hours or more after the use of anesthetic therapy, including the cases in whom SE recurs on weaning of anesthesia. [1]

RSE occurs in 23%–43% and SRSE in approximately 22% of the patients with SE. [2,3] The causes of RSE in adult population in developing countries is presumed encephalitis, which is more common in children than in adults and elderly. [4] CNS vascular etiology is more commonly seen in adults and elderly, whereas metabolic etiology predominates in elderly population. In the developed countries, the commonest etiology is stroke followed by drug withdrawal. [5] The treatment of RSE and SRSE includes benzodiazepines, sodium valproate, phenytoin, levetiracetam, and anesthetic drugs such as midazolam, phenobarbital, and propofol that may produce hypotension and respiratory suppression; therefore, patients with RSE should be managed in intensive care units (ICUs). [4]

Sudden unexpected death in epilepsy (SUDEP) is defined as “death in a patient with epilepsy that is not due to trauma, drowning, SE, or other known causes but

for which there is often evidence of an associated seizure" and represents a leading cause of death in patients with epilepsy. [6]

Approximately 0.4–1 per 1000 of epileptic patients die from SUDEP with a mortality rate that increases to 9.3% when referring only to patients who have refractory epilepsy. SUDEP has been reported in many populations, from young children to the elderly. The highest prevalence of SUDEP is in people between the ages of 20 and 45. [7] Although the exact mechanisms of SUDEP are unclear, arousal dysfunction after a generalized seizure, secondary cardiac arrhythmias (bradycardia and asystole) and postictal apnea are amongst few of the proposed ones. [8]

SE is an important neurological and medical emergency and itself is a known independent risk factor for mortality, but cardiac complications also contribute to worse outcomes along with increased risk of mortality. [9-14] Common cardiovascular disease risk factors, such as diabetes mellitus (DM), hypertension, dyslipidemia, and heart failure, are prevalent in patients who suffer from SE and may determine the chronicity of cardiac complications. [15-17] However, even in the absence of coronary artery disease, cardiovascular dysfunction is possible in patients of SE. [14] Hypotension occurs frequently in this population and is generally attributed to the use of anaesthetic agents; however, in some cases it may result directly from neurocardiogenic injury. Markers of cardiac injury are commonly raised in RSE such as troponin levels. ECG findings including ST elevation, ST depression, new T-wave inversion and nonspecific ST changes, can also be seen in SE. Cardiac arrhythmias which are frequent in SE includes ventricular tachycardia (V tach) /ventricular fibrillation (VF), atrioventricular block (A-V block), atrial fibrillation (AF)/ atrial flutter (AFL), sinus bradycardia, and sinus tachycardia for which intervention are required. Corrected QT interval (QTc) prolongation has also been noticed in such patients. 2D Echo when obtained mostly showed normal left ventricular (LV) and right ventricular (RV) function. However generalized LV and RV dysfunction, and inferior regional wall motion abnormalities (RWMA) have also been witnessed. [11] Postictal arrhythmias may also be a marker of an increased SUDEP risk. [18] Over the last

few decades, many seminal animal studies have been done to study association of cardiac injury in SE and RSE. However, animal data is difficult to translate to humans studies. Therefore, this study was planned to diagnose early cardiac injury in patients of SE and RSE with special focus on non-invasive diagnostic modalities like ECG, Holter, 2-D Echo and cardiac enzymes i.e Troponin I (Trop I) and N-Terminal pro b-type natriuretic peptide (NT Pro BNP).

REVIEW OF LITERATURE

SE is a heterogeneous group of disorders with various clinical presentations and etiologies. It is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1). It can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures. As per the ILAE Task Force on Classification of SE, for tonic-clonic SE, t_1=5 min, and t_2=30 min, for focal SE with impaired consciousness t_1=10 min, and t_2>60 min, and for absence SE t_1=10-15 min, and t_2 is unknown. [1] Refractory SE is defined as SE that fails to respond to adequately used 1st (BDZ) and 2nd line (appropriately chosen non- BDZ) medications. [19] Further, super-refractory SE is SE that persists for 24 hours or more after initiation of 3rd line medications (anaesthetics) or recurrence of seizure during withdrawal of the anesthetics. [20] Additional terminologies in RSE include NORSE and FIRES. NORSE is new onset of refractory SE without a clear acute or active structural, toxic, or metabolic cause in a patient without active epilepsy or other preexisting relevant neurological disorder. It is a clinical presentation and not a specific diagnosis. FIRES is a subcategory of NORSE with a prior febrile infection between 2 weeks and 24 hours prior to onset of refractory SE, with or without fever at the actual onset of SE. [1]

Demographics of RSE

SE is a frequent neurological emergency associated with an annual incidence between 10-41 per 100,000 individuals. The incidence of SE has a bimodal distribution with peaks in children aged less than a year and the elderly. [21] Estimated frequency of RSE in patients with SE ranges from 31-44%. [3,9] RSE affects more men than women. In a systematic study, the female to male ratio has been found to be 1.19:1. The mean age of RSE onset ranges from 0-92 years with mean age of onset is 39.8 ± 25.9 years.

Epidemiology of RSE

There is geographical difference in the incidence and prevalence of RSE with high frequency in Europe, Asia, United States of America, New Zealand, and Australia. Patients from Asia were significantly younger than those from Europe and the Americas (mean age= 22.4, 48.2, and 40.5 years, respectively, $P < .001$) and more frequently presented with convulsive SE (CSE) compared with non convulsive forms (71%, 53%, and 44%, respectively, $P < .001$). The ICU duration was longer in Asia (mean = 22.8 ± 24.1 days) than in Europe (16.3 ± 18.9 days) or in the Americas (19.31 ± 26.3 days) ($P < .05$). [20]

Differences were noted regarding etiologies of SE. In Asia, the infections (30.1%) were the most frequent reported etiology, whereas infections represented only 15.4% of cases in the Americas and 12.3% of cases in Europe. In infections, acute encephalitis cases were significantly higher in Asia (20.9%) than in Europe (5.7%) or the Americas (4.7%). Vascular etiologies were more frequent in Europe (16.6%) than in Asia (5.6%), and traumatic etiologies were higher in Europe (6.2%) and the Americas (4.7%) than in Asia (0.5%). [20]

Epidemiology of RSE in India

The incidence of RSE in India was estimated to be approximately 22.9% as per study done by Kohli et al in 2017. [22] In the same study, the incidence of SRSE was 7.8%. Two hundred and eighteen patients were included in the study. There were 114 (52.3%) males, bimodal age preponderance with 30% having age <5 years, and second peak (52.8%) in age 15–65 years. Preexisting seizures were seen in 34.4% and 22.9% had RSE ($n = 50$). [22]

Causes and risk factors

Any pathology that can cause an acute symptomatic seizure, can also lead to SE that may eventually progress to RSE/SRSE. The underlying causes of SE as given by ILAE 2010 are divided as known or symptomatic and unknown i.e. cryptogenic. [33] The “known” or “symptomatic” etiology for SE can be structural, metabolic, inflammatory, infectious, toxic, or genetic. Based on its

temporal relationship, the subdivisions of acute, remote, and progressive are applied to known causes of SE. The term “unknown” or “cryptogenic” is used in its strict meaning for unknown cause.

Infectious Causes

The etiology of RSE/SRSE varies geographically, and studies from India have noted a predominance of infectious causes. In a study done by Mishra et al on 148 adults with encephalitis, 18 were diagnosed with SE, predominantly in those with herpes simplex virus (HSV) infection or Japanese encephalitis. [24] Infections are found to be more frequent in children than adults. Elderly patients, on the other hand, have a significantly higher incidence of metabolic etiology compared to adults and children. Additionally, there is a paucity of data on epidemiology of RSE/SRSE from India in other common infections including acute bacterial meningoencephalitis, cerebral malaria, and dengue.

Autoimmune and Genetic Etiologies

The leading autoimmune entity associated with RSE is anti- N-methyl-D aspartate (NMDA)-receptor encephalitis, which can present with non-specific manifestations, such as fever or headache in the prodromal stage. The next stage involving the cerebral cortex is the one, which can present with RSE/SRSE in additional to behavioral symptoms. The behavioral phenotype of limbic encephalitis in adults often consists of disturbances in recent memory, and affective symptoms including irritability, depression, or hallucinations. Compared to the predominant temporal localization for seizures in adults with anti-NMDAR encephalitis, extra-temporal seizures, and sometimes even diffuse bilateral ictal onset can be seen and should not exclude this consideration. [25]

The other important etiologic subgroup of RSE/SRSE, which should be evaluated promptly, comprises of certain genetic epilepsies. These include sodium channelopathies, ring chromosome 20, pathogenic variants in polymerase-G or amino-acyl-tRNA synthetase genes affecting mitochondrial function, and Angelman syndrome.

Seizure Triggers

About 16-38% SE episodes occur in children with a prior diagnosis of epilepsy, with low anti-seizure medication levels being the most common risk factor. Low levels of regular anti-seizure medicines can, in turn, result from lack of adherence, scheduled withdrawal, insufficient dose, interaction with other concurrent medications, or growth spurt. Other common precipitants of SE include inter-current illness, exposure to a known trigger (e.g. sleep deprivation in some idiopathic generalized epilepsy syndromes), or metabolic decompensation. [25]

Etiological analysis for SE by Cascino et al in 2017 revealed that central nervous system (CNS) infection was the most common cause constituting 32% followed by metabolic derangements in 12.8%, idiopathic in 11.5%, cerebrovascular accident (CVA) in 9.6%, and autoimmune encephalitis in nearly 8%. [26] Other etiologies included ASM withdrawal, breakthrough seizures, poisoning, trauma, and congenital malformations. [22] In another study, Cascino et al described CNS infections in 17%, hypoxia in 20%, CVA in 18%, unknown in 14%, and others less than 10%. [26]

Acute symptomatic seizures were seen in 19.3%, 19.3% with remote symptomatic, and 5.5% with cryptogenic SE, respectively. In a prospective study in Richmond, Virginia, remote symptomatic etiology was observed in 39% of children and 24% of adults, whereas acute symptomatic etiology was seen in 52% of children. [27] In another study Novy et al, described acute symptomatic, remote symptomatic, and cryptogenic seizures in 59%, 17%, and 8% of patients, respectively. [28] An audit on SE from India had found 60% as remote symptomatic and 16% acute symptomatic cases. [29]

Pathophysiology of RSE

SE is result of failure of Gamma Aminobutyric acid (GABA) receptor-mediated inhibition, which may be responsible for the normal termination of a seizure. Another mechanism is that the activation of NMDA receptor by excitatory neurotransmitter glutamate may be required for the propagation of seizure activity.

RSE has been attributed to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive NMDA excitatory receptor-mediated transmission. In experimental models, resistance to both benzodiazepines and barbiturates develops during prolonged seizures and it has been hypothesized that prolonged seizure activity alters the structure and/or function of GABA-A receptors.

SE induced neuronal death is initiated by excessive glutamate release, which activates postsynaptic NMDA receptors and triggers receptor-mediated calcium influx (excitotoxicity) leading to necrosis and cell death. These proposed dramatic alterations in inhibitory and excitatory pathways have important role for pharmacological management of SE. Drugs shown to be effective in RSE act not just on benzodiazepine receptor sites, but also acts on other sites. Propofol acts at a site distinct from the benzodiazepine and barbiturate binding sites, while isoflurane acts by potentiation of inhibitory postsynaptic GABA-A receptor-mediated currents, although effects on thalamo-cortical pathways also have been implicated. [30]

Clinical Features

Prodromal Symptoms

Gaspard et al observed that 75 of 125 cases (60%) exhibited prodromal symptoms preceding the onset of NORSE, including fever (34%), confusion (45%), headache (22%), fatigue (26%), symptoms of a gastrointestinal (18%) or upper respiratory (13%) tract infection and behavioral changes (16%). [32] In addition, some patients may experience the following symptoms: memory complaints, language difficulties, hallucinations, rash, and arthralgia.

Seizure Types

In a series of 125 patients with NORSE, 13 patients (10%) experienced simple partial seizures, 36 (29%) experienced complex partial seizures, and 83 (67%) experienced tonic-clonic seizures. [32] Thirty patients (28%) presented as SE before admission, 16 (15%) presented as complex/simple partial SE, and 19 (13%)

as generalized convulsive SE (GCSE).

GCSE is the most urgent and serious type, presenting with persistent limb rigidity and clonic or tonic-clonic seizures with dysfunction of consciousness. Wilder-Smith et al reported six cases among seven patients who presented a generalized seizure-type SE, and the EEG showed multifocal seizures. [33] In the study by Khawaja et al, 90% of patients experienced GTCS. [34]

Simple Partial Seizures

Peter et al reviewed six children aged 5 months to 6 years who presented with focal seizures that progressed to intractable multifocal seizures with or without secondary generalization within days; the seizures recurred every few minutes and persisted for weeks. Four patients displayed simple partial seizures with twitching/rotation of their arms; the seizure frequency increased within 1–3 days and ultimately resulted in erratic myoclonus and tonic seizures. These patients later developed RSE. Van Lierde et al reported a 30-year-old woman who presented with simple partial seizure, including right facial twitching, left eye deviation, blinking and hypersalivation, and clear consciousness with EEG showing right temporal lobe seizures. [35]

Complex Partial Seizures

Costello et al reported a case study of six patients with NORSE. [36] Two patients showed an abrupt onset of non-convulsive complex partial SE without generalized convulsive activity. Confused behavior with obtundation and intermittent focal motor seizure activity were the main clinical manifestations.

Secondary GTCS

Many publications have described patients with NORSE who initially present as partial seizures, followed by GTCS that are designated as secondary GTCS. Van Lierde et al examined six young patients and showed that 5 patients exhibited partial seizures, such as head and eye deviation, facial twitches, aphasia, blinking, and hyper salivation. [35] Later, the patients developed secondary GTCS.

Absence Seizures

Absence seizures have not been reported in the literature till date with SE.

RSE in patients with preexisting epilepsy

Patients with RSE who had a preexisting epilepsy diagnosis present with variety of seizure types. Miyahara et al retrospectively analyzed nine patients with RSE who were diagnosed with progressive myoclonic epilepsy before and had a pre-existing epilepsy diagnosis. [37] The RSE types included in the study were myoclonic SE (n = 3), myoclonic generalized SE (n = 4), and generalized SE (n = 2). Tassinari et al studied 5 patients with Lennox-Gastaut syndrome (8–17 years old, three males and two females) who had pre-existing epilepsy, tonic SE *(n=3),* atonic attack *(n=1),* and myoclonic atonic *(n=1).* [38]

Nobutoki et al reported seven refractory NCSE episodes in 5 patients who had a history of epilepsy. [39] Two patients were diagnosed with Lennox-Gastaut syndrome and the other three patients with symptomatic generalized epilepsy, continuous spike-waves during slow-wave sleep, and ring chromosome 20 syndromes, respectively.

Refractory status in Hypoxic Ischemic Encephalopathy (HIE)

Sutter et al reported that of RSE occurring after HIE; NCSE was observed in 65%; simple partial seizures, complex partial seizures, and absence seizures accounting for 29.26% of NCSE. [40]

Refractory status in infections

The seizures reported in literature are primarily partial seizures, partial secondary generalized seizures, and generalized seizures. In one case study, 34 patients with bacterial meningitis presented with seizures in the acute phase and ten of these patients developed SE. [41] Most of the observed seizures were secondary tonic-clonic seizures. In a separate study performed in Spain that included 38 patients, 8 of the patients had generalized seizures, 23 had partial seizures, and two had partial secondary generalized seizures. [42] Finally, a study of 107 patients with both

bacterial meningitis and seizures revealed that 20% had partial seizures, 21% had partial secondary generalized seizures, and 59% had generalized seizures. [43]

Time of Epilepsy or SE Onset

Seizures can occur during both the acute phase and the recovery phase in bacterial meningitis. The former is called acute symptomatic epilepsy, and the latter is called delayed epilepsy. In a study performed in the Netherlands, seizures occurred within 48 hours of admission in approximately 75% of 696 patients with bacterial meningitis. In another study that included 218 children with SE, the initial seizure was SE in 71% of the episodes and was associated with an acute etiology (28% had bacterial meningitis). [44] A study of 116 patients with bacterial meningitis and seizures, including 17 with SE, showed that the seizures occurred during the acute phase of infection. [45] Sixty-one of the patients did not develop seizures during the acute phase, and these patients did not develop delayed epilepsy. Fifty-five of the patients developed seizures during the acute phase, and 11 of these patients developed delayed epilepsy. Fourteen of the 34 patients who developed seizures in the acute phase and were followed for an additional 18 months also developed delayed RSE. [41] Therefore, SE that occurs during the acute phase is a risk factor for delayed RSE.

Management of RSE

The first steps of SE treatment run in parallel with diagnostic procedures. After attending to pulmonary and cardiac dysfunction, control of seizures is priority and generally follows the intravenous administration of a sequence of three groups of drugs: benzodiazepines aimed at rapid SE control, classic ASMs targeted at early resistant forms and long term coverage, and general anaesthetics for RSE. [46,47,48] Benzodiazepines are the only evidence-based treatment, as shown in three trials and a Cochrane review. However, only one trial has been done to compare them with other medications and lorazepam had statistically better results than phenytoin. [49]

The overall aggressiveness of treatment depends on the type of SE. GCSE should

be treated aggressively in view of the danger of systemic and neurological injury with ongoing seizures. [19] The precise criteria for induction of coma for the treatment of focal complex SE is debated because the treatment can lead to various complications, such as infections (many patients with mechanical ventilation develop pneumonia) or drug side- effects, ileus, neuropathy, myopathy, thrombosis, and embolic events, to cite only the most frequent. [48, 50-54] Therefore, these risks should be balanced against the benefit of rapid seizure control. The validated clinical SE severity score (STESS) can help to orient early treatment strategy. [49,50] With four variables (age, seizure semiology, extent of consciousness impairment, and history of previous seizures, as a surrogate for cause), the STESS is readily applicable in emergency settings, relies on straightforward clinical criteria, and has a robust negative predictive value for mortality (i.e. patients with a low score are very unlikely to have a fatal outcome). Thus, to proceed straight to third-line, coma-inducing treatment seems reasonable if the second-line treatment with intravenous antiepileptic agents (which take at least 20–30 min to be effective) has failed in patients with GCSE (who have a high STESS). [46] Conversely, at least in some patients, focal RSE without major impairment of consciousness (and therefore a low STESS) can initially be managed without anaesthetic agents for the first 24–36 hours.

Mortality in RSE

In the recent studies the reported mortality rates varied between 16 to 23%. [13,19] In a retrospective study, the outcome was independent of specific coma inducing agents used and the extent of EEG burst suppression, suggesting that the underlying cause represents its main determinant. [55] RSE had a mortality rate of about 35% in one pooled review, and SRSE has a mortality of 30% to 50% in various studies. [56] Mortality after RSE is about three times higher than for non-refractory SE. [57,19]

For most late fatalities, the reason is the underlying clinical triggers. [32] Along with age, etiology is consistently identified as the principal independent outcome predictor. [32,20] In an Indian study presumed encephalitis followed by

autoimmune etiologies had higher mortality[70] Stroke-induced RSE has a poor prognosis and high mortality [62]. In another study, post anoxic encephalopathy and brain tumors were independently associated with the increased rate of death [20]. Withdrawal from ASMs, an acute cause is often related to good outcome, and primary brain tumor as a remote cause with poor prognosis. [32,18]

Lower levels of consciousness (coma or stupor) at the onset of SE are more likely to result in mortality. Also, GCSE and NCSE were independently associated with death. [56,32] Duration of RSE and duration of coma greater than ten days also have an unfavorable outcome. [55] EEG findings of periodic epileptiform discharges are more frequently associated with poor outcome in RSE. [79] On the contrary, the absence of burst suppression and isoelectric EEG is associated with good outcome possibly due to the reduced burden of anesthetic medications and decreased duration of coma and hospitalization. [55]

Cardiac manifestation in RSE

Cardiac manifestations frequently occur during seizures but are typically benign. Continued tonic-clonic seizure activity, termed CSE, results in sympathetic nervous system overactivity, which may lead to myocyte damage, cardiac contractile dysfunction and susceptibility to arrhythmias. [57] In an autopsy study, death from SE was significantly associated with the presence of cardiac contraction bands, presumably due to massive catecholamine release during seizures. [58]

Hocker et al in 2017, identified 59 consecutive patients with RSE of which 35 patients demonstrated markers of cardiac injury. [11] Twenty-three patients had troponin levels drawn at onset of SE, of which nine were abnormal. ECG findings at onset of SE included ST elevation (11.4%), ST depression (5.7%), new T-wave inversion (37.1%), and nonspecific ST changes (37.1%). Cardiac arrhythmias included V Tach /VF (11.4%), AV block (2.9%), AF/AFL (20.0%), sinus bradycardia (48.6%), and sinus tachycardia (65.7%). Intervention was required for cardiac arrhythmias in 42.9%. QTc was prolonged in 22.9% of patients. One patient had non–ST-elevation myocardial infarction (NSTEMI). Of 14 patients

evaluated with ECG during SE, 3 demonstrated reversible systolic dysfunction. In-hospital mortality was 34.3%. Outcome was worse in the group with markers of cardiac injury but was not statistically significant. [11]

In a review article by Lende et al, different types of ictal and post ictal arrhythmia patterns were identified in 126 cases, ictal asystole being the most frequent (44%). [18] Ictal asystole, ictal bradycardia and ictal AV block predominantly occurred during focal dyscognitive seizures in people with temporal lobe epilepsy. Postictal arrhythmias including asystole, AV block and the less prevalent AF and VF usually occurred after a convulsive seizure and were frequently associated with SUDEP. Postictal arrhythmias had greater importance to the pathophysiology of SUDEP rather than ictal arrhythmias.

Kurukumbi et al conducted a retrospective study of ECG changes in SE in 2014 on 113 African American patients of more than 15-years of age. [59] ECG changes were assessed within 6 hours and after 24 hours in patients with SE. ECG changes were present in 84% of patients within 6 hours of SE. The most frequently observed ECG abnormalities were ischemic patterns, conduction abnormalities and arrhythmias both within 6 hours and more than 24 hours. The most common ischemic changes were T wave changes appreciated in 16 patients, followed by ST depression in 10, ST elevation in four, poor R progression in four and new Q waves in two patients. Conduction abnormalities were seen in 28 patients within 6 hours and 7 patients after 24 hours. The types of arrhythmias observed included premature ventricular contractions in six patients, AF in five patients, AFL in three patients, junctional rhythm in three patients and premature atrial contractions in two patients. Of the 95 patients (84%) with ECG changes, 61 had persistent ECG changes.

Boggs et al in 1992, reviewed electrocardiograms of 60 patients presenting in SE. [60] The most frequently observed ECG abnormalities were ischemic patterns. Axis changes, conduction abnormalities and miscellaneous rhythm abnormalities also occurred. ECG changes occurred most frequently during SE with decreasing occurrence of abnormalities at longer intervals from SE. These ECG changes were

statistically significantly associated with mortality. Sequential ECGs before, during and after ictal episodes were compared to define changes from baseline studies. 58.3% of the SE patients exhibited significant abnormalities on ECG when obtained within 24 hours of SE.

Reduced HRV is an accepted individual biomarker for mortality for sudden death in heart disease and is hypothesized to be a biomarker for SUDEP [61,62] Out of limited data that has been published regarding HRV in RSE, Laniger S et al retrospectively reviewed 53 adult patients in 2006-2007 collecting EEG along with the heart rate data including R-R intervals and SDNN. There was a statistically significant difference between the two groups. In the patients with non-status EEGs, the SDNN observed was an average of 41.4 ms, while in SE it was much lower as 20.5ms. The significantly reduced SDNN was suggestive of decreased HRV seen in SE. [63]

AIM AND OBJECTIVES

AIM OF STUDY

To assess cardiac abnormalities in patients of RSE.

OBJECTIVES OF STUDY

PRIMARY OBJECTIVE

To assess markers of cardiac injury, ECG and 2D Echo changes in patients of RSE.

SECONDARY OBJECTIVE

1. To correlate cardiac abnormalities (Trop I, NT Pro BNP, ECG and 2D Echo) within 24-hours of RSE with prognosis of patients at discharge/death and at 30-days.

2. To assess for new changes or persistence of cardiac abnormalities (ECG and 2D echo) at 30-days with functional outcome.

MATERIALS AND METHODS

STUDY SETTINGS

This study was carried out among patients of RSE admitted in the Department of Neurology at All India Institute of Medical Sciences, Jodhpur, Rajasthan. This study was conducted in collaboration with Department of Cardiology and Department of Anaesthesiology and Critical care, at the same institute.

STUDY DESIGN

This was a prospective, observational, cohort study.

STUDY PERIOD

January 2021– June 2022 (18 months).

SAMPLE SIZE

Based on the past experience we estimated to receive approximately 25-30 patients with RSE presenting in the acute phase to be evaluated at the baseline on admission and further followed up at discharge or death and 30 days post discharge. However, due to the global pandemic of COVID-19 and our institute being a dedicated COVID-19 facility, we could only recruit 20 patients over a span of 18 months. These were followed up at discharge and 30 days post discharge.

STUDY METHODOLOGY

This prospective, observational, cohort study was carried out after obtaining ethical clearance certificate number AIIMS/IEC/2021/3401 dated 12/03/2021 from the institute's ethics committee. Informed written consent was obtained from all the patients

All patients were recruited in the study during the acute phase of RSE regardless of etiology. RSE was defined as SE persisting despite sufficient dose of benzodiazepines and at least one ASM, irrespective of time. [1]

Patients with past history of cardiac implants or known cardiac illness were excluded as this study evaluated cardiac changes in the first 30 days of patients with RSE.

Detailed demographic information of all the patients was collected. Clinical details with general physical and neurological examination were done. Information regarding onset, progression, course, probable etiology of the SE, other risk factors and previous treatment history was enquired from all the patient attendants.

Laboratory evaluations constituted MRI Brain and cerebrospinal (CSF) analysis. CSF examination for cell cytology and biochemistry was done as per the clinical and radiological characteristics of the disease. Additional biochemical studies were undertaken as and when dictated by the clinical and radiological features.

All patients with RSE were monitored with continuous bedside EEG for the first 24 hours and on a daily basis thereafter. Additionally, they were evaluated in detail regarding the cardiac parameters. All patients underwent NT pro BNP, Trop I test, 6 hourly ECG, 24 hour Holter and 2D Echo. Follow-up cardiac studies were also undertaken- NT pro BNP, Trop I test, ECG, 2D Echo at discharge and ECG, 2D Echo at 30 days post discharge.

STUDY PARTICIPANTS

INCLUSION CRITERIA

1. Patients with age of 18 or more with or without comorbidities.
2. Patients fulfilling diagnostic criteria of RSE. [1]
3. Patients willing to provide written informed consent.

EXCLUSION CRITERIA

1. Patients with Coronary Artery Disease or Ischemic Heart Disease.
2. Patients with Heart failure/cardiomyopathy.

3. Patients with Congenital Heart disease

4. Patients with past history of pacemaker /Implantable Cardiac Defibrillator

TOOLS

1) Clinical History

Demographic details of the patients like name, age, gender, residence, education and occupational status were recorded. Detailed clinical history including cause and duration of SE were collected along with details of general physical and neurological examination including Glasgow Coma Scale (GCS) and modified Rankin Scale (mRS). Additional variables regarding RSE were collected: type of refractory status (convulsive or non-convulsive), duration of seizure, seizure frequency, number and type of ASM taken, whether known case of epilepsy or de-novo seizures, prior history of seizures/ SE and neuroimaging.

2) Continuous bed side EEG

All the patients were admitted in ICU and continuous EEG recording was done using the 10-20 International system of electrode placement. The EEGs were assessed based on background rhythm, pattern of discharges, burst suppression and the presence of any electrographic seizures. NCSE was defined as changes in behaviour and/or cognition from baseline and diagnosed according to Salzburg criteria and divided into definite, probable and possible NCSE. [64]

Electrographic seizures were also noted and defined as a rhythmic discharge or spike and wave pattern with definite evolution in frequency, location, or morphology lasting at least 10 seconds; evolution in amplitude alone did not qualify. [65]

Burst suppression was used to describe an EEG pattern consisting of a continuous alternation between high-voltage slow waves (occasionally sharp waves) and depressed (or suppressed) electrographic activity. [66] In case of presence of burst suppression pattern, the duration of the burst, suppression and inter burst interval was noted.

3) Cardiac Monitoring

a. ECG monitoring:

ECG was done immediately on presentation and 6 hourly in the first 24 hours of RSE. Arrhythmias such as AF/AFL/VF/ VFL, sinus arrhythmia, sinus pause and asystole were included in our study. We defined a sinus pause as a clearly visible delayed sinus beat, where the following beat is exactly in line with the original rhythm and there is no other visible irregularity in heart rhythm. An asystole was defined as a period without heart beat nor 'p' wave lasting at least 3 seconds. Conduction abnormalities included AV-block and bundle branch block (QRS-complex widening of more than 0.12s). Repolarization abnormalities comprised of T wave inversion and ST-elevation or depression (equivalent to >2 mm). Bradycardia was defined as heart rate less than 60 beat per minute, tachycardia as heart rate more than 100 beat per minute, significant tachycardia has been taken as more than 150 beats per minute and QTc prolongation as QTc more than 450 msec in males and more than 460 msec in females.

b. Cardiac enzymes:

For cardiac enzyme analysis in all the patients, quantitative analysis was done used. Result was noted for whole blood sample. Trop I more than 0.5 mg/ml and NT pro BNP more than 150 pg/ml was taken as abnormal.

c. Holter monitoring:

For holter monitoring, a 24-hour study was done and analysed in all the patients. The changes noted were for sinus tachycardia, sinus bradycardia, AF, AFL, VFL, VF, QTc interval, ventricular/supraventricular ectopics and HRV.

For HRV, standard deviation of inter beat interval of normal sinus beats (SDNN) and root mean square of successive differences between normal heartbeats (RMSSD) were studied in 24 hours domain as per the European Society of Cardiology and North American Society of Pacing And

Electrophysiology. [67] SDNN is the mean of the SDs for all R–R intervals, and RMSSD is the root mean square differences of successive R–R intervals. Normative value for SDNN (mean+/- SD) was taken as 141+/-39 ms and for RMSSD as 27+/-12 ms. [68] SDNN less than 100 ms was taken as abnormal.

d. *2D Echo*

Bedside 2D Echo was done for all the patients by the cardiologist. The parameters assessed for were- regional wall motion abnormality, valvular defects, atrial and/or ventricular dilatation, LV and/or RV dysfunction.

CARDIAC INJURY

Patients were divided into two groups: those with cardiac injury including transient LV/RV systolic/diastolic dysfunction, T-wave inversion, ST elevation or ST depression, QTc prolongation, and/or elevated Trop T or NT pro BNP levels, and without cardiac injury (no markers of injury). Arrhythmias were not considered directly representative of cardiac injury.

OUTCOME

Outcomes were determined by mRS, and GCS at hospital discharge and 30 days after discharge.

Poor functional outcome was defined as mRS score of 4 or higher at discharge and follow up.

ETHICAL CONSIDERATION

Informed written consent was taken from all the study subjects. No pressure or coercion was exerted on subjects for participation in the study. Enrolment in the study did not pose any additional risk to the patient. Ethical approval was taken from the institutional ethics committee.

STATISTICAL ANALYSIS

All the collected data was entered in Microsoft Excel sheet and analyzed using SPSS 27.0.1. A value of $P < 0.05$ was considered significant for all statistical tests.

Descriptive statistics and univariate analysis was performed.

We compared various demographics, etiology parameters, cardiac injury, cardiac arrhythmias and reduced HRV with mortality at discharge and at 30 days follow up by Fisher exact test. The variables found to have significant p value, were analysed using multivariate logistic regression analysis and odds ratio among these independent variables were calculated.

OBSERVATIONS AND RESULTS

This study was carried out among patients of RSE admitted in the department of Neurology at All India Institute of Medical Sciences, Jodhpur, Rajasthan over a period of 18 months from January 2021 to July 2022 in collaboration with the department of Cardiology and department of Anaesthesiology and Critical care. Patients were recruited after due informed consent from their attendants. All patients were admitted in the intensive care unit for management of RSE. After this, patients underwent ECG, 2D Echo, Trop I, NT pro BNP, 24 hour holter monitoring and continuous EEG monitoring. On the basis of presence or absence of either of the parameters namely LV dysfunction, T wave inversion, ST elevation, ST depression, raised Trop I and raised NT pro BNP, the patients were divided into two groups- Group A- Cardiac injury group and Group B- Non cardiac injury group.

Demographics of study population

Demographic details of the patients like name, age, gender, residence, education and occupational status was obtained. A total of 20 patients of RSE were included in the stud **o**f total 20 (100%) patients studied, 10 (50%) were female and 10 (50%) were male (Figure 1).

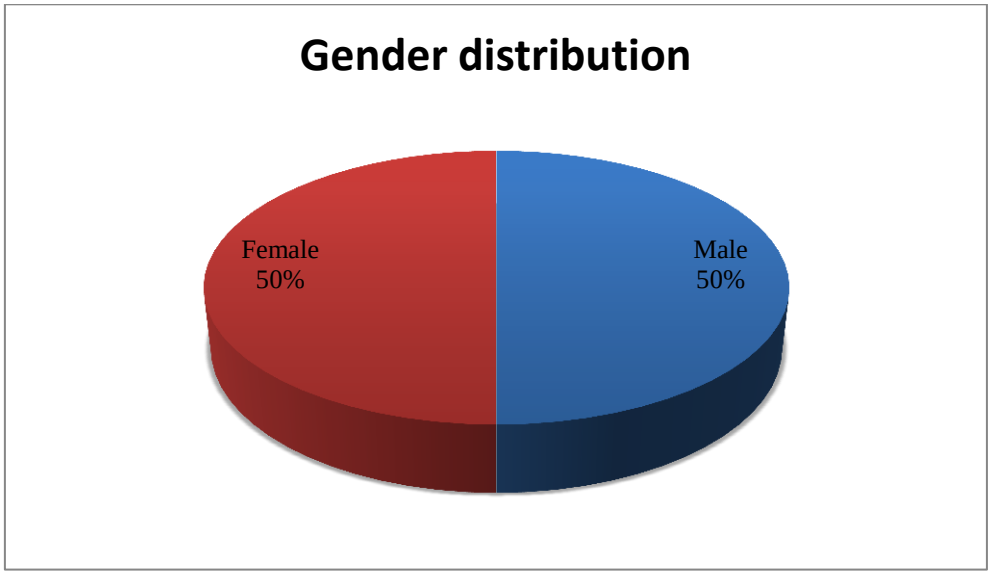


Figure 1: Distribution of the study population on the basis of gender

Of the total 20 (100%) patients studied, the most common presenting age group was 31-40 years (6 patients). Three (5%) patients were 21-30 years of age. RSE did not show predilection for any specific age group as there were 4 (20%) patients in 51-60 years age group and 4 patients (20%) in the age group 61-70 years. Mean age of presentation was 47.75±17.2 (range: 22-80) years and median age 46 years (range: 22-80). (Table 1)

Table 1: Distribution of study population on the basis of age

NO.	AGE GROUP (YEARS)	NO. OF PATIENTS N (%)
1.	**21-30**	3 (15)
2.	**31-40**	6 (30)
3.	**41-50**	2 (10)
4.	**51-60**	4 (20)
5.	**61-70**	4 (20)
6.	**71-80**	1 (5)
	Total	20 (100)

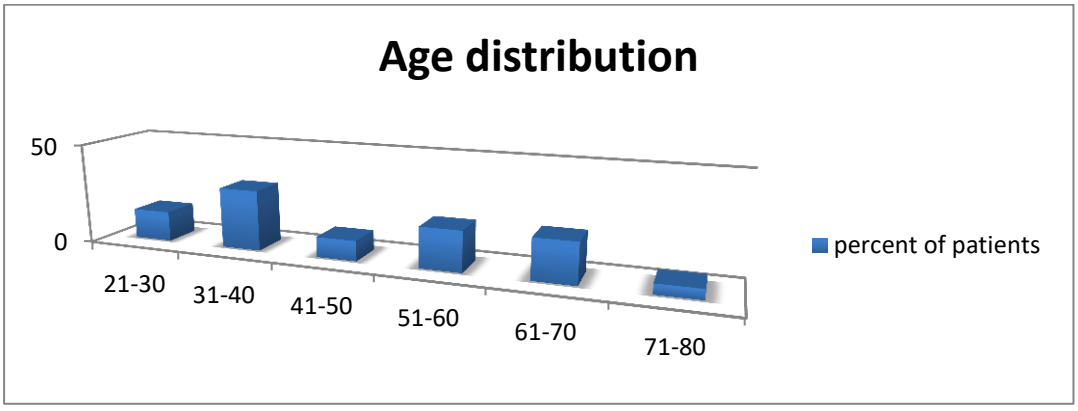


Figure 2: Distribution according to age group

On studying the educational status in our population, it was found that 8 (40%) had education up to middle and high school or more and only 2 (10%) were graduate and above Illiteracy was found in 8 (40%) patients. (Table 2)

Table 2: Distribution of study population on the basis of educational status

NO.	EDUCATION	NO. OF PATIENTS N (%)
1	Illiterate	8 (40%)
2	Primary	2 (10%)
3	Middle	4 (20%)
4	High School	4 (20%)
5	Graduate And Above	2 (10%)
	Total	20 (100%)

On studying these patients for socio-economic status, it was found that 11 (55%) belonged to lower class according to modified Kuppuswamy classification for socio-economic status, while only 4 (20%) belonged to lower middle and 5 (25%) to upper lower class and none of the patients belonged to upper or upper middle class. (Table 3)

Table 3: Distribution of study population on the basis of socio-economic status

NO.	SOCIO- ECONOMIC STATUS (MODIFIED KUPPUSWAMY)	NO. OF PATIENTS
1	Upper	0 (0%)
2	Upper Middle	0 (0%)
3	Lower Middle	4 (20%)
4	Upper Lower	5 (25%)
5	Lower	11 (55%)
	Total	20 (100%)

On studying the employment status, it was found that 4 (20%) patients were unemployed, 2 (10%) were semiskilled worker, 10 (50%) were farmer and 4 (20%) were house wives. (Figure 3)

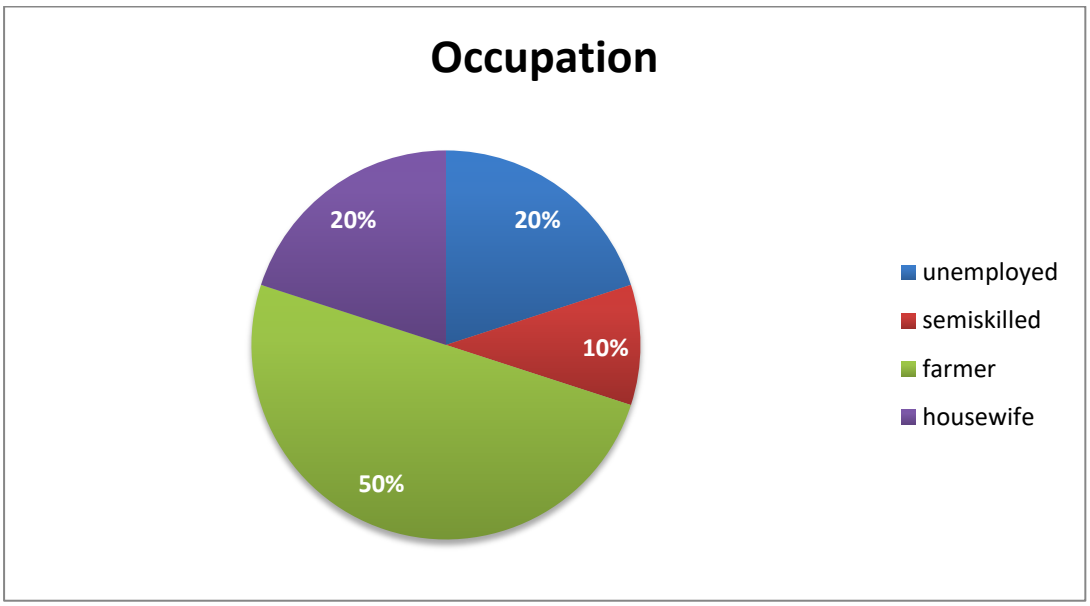


Figure 3: Distribution according to occupation

Clinical features in study population

Time-line of presentation

On studying the population for clinical presentation at the time of acute episode, it was found 11 (55%) patients presented within first 24 hours of onset of disease. Out of these 11 patients, 10 presented between 12-24 hours and only one patient could manage to reach emergency department within 12 hours. (Table 4) Three (15%) patients presented in 36-48 hours, and remaining 6 (30%) presented late between 60-72 hours after onset of disease. The mean time within which patients got admitted after onset of disease was 40.50 ±25.667 hours.

Table 4: Distribution according to time lag from onset of disease to admission

ONSET OF DISEASE TO ADMISSION (HOURS)	NO. OF PATIENTS N (%)
0-12	1 (5.0%)
12-24	10 (50.0%)
36-48	3 (15.0%)
60-72	6 (30.0%)
Total	20 (100%)

Subsequently studying the time interval between presentation in ER and onset of seizure, it was found 17 (85%) patients presented within the first 12 hours. Of these 17 patients, 10 (50%) patients presented within 6 hours and 7 (35%) patients could manage to reach ER within 6-12 hours. The mean time within which patients got admitted after onset of seizure was 8.80 ± 7.024 hours and median 6.50 hours (range 1-48). One patient had gone into RSE after 6 hours of admission. (Table 5)

Table 5: Distribution according to time lag from onset of seizure to admission

ONSET OF SEIZURE TO ADMISSION (HOURS)	NO. OF PATIENTS N (%)
1-2	3 (15.0%)
2-6	7 (35.0%)
6-12	7 (35.0%)
12-18	2 (10%)
18-24	1 (5.0%)
Total	20 (100%)

GCS at presentation

At presentation, the GCS in these patients of RSE showed 13 (65%) patients had GCS score less than 8 suggestive of poor GCS (Table 6). Out of these 13 patients, 4 (20%) patients had GCS of 3 and rest 9 (45%) had GCS of 4-8. Seven (35%) patients had good GCS 9-15 at the time of presentation. (Table 6)

Table 6: Distribution according to GCS at admission

GCS AT PRESENTATION	NO. OF PATIENTS N (%)
3	4 (20.0%)
4-8	9 (45.0%)
9-15	7 (35.5%)
Total	20 (100.0%)

mRS at presentation

At the time of admission mRS was calculated for all the patients and 17 (85%) patients had mRS 5 two (10%) patients had mRS 4, one (5%) patient had mRS 1 and none had mRS 2 or 3 at presentation. (Table 7)

Table 7: Distribution according to mRS admission

mRS AT PRESENTATION	NO. OF PATIENTS N (%)
1	1 (5.0%)
2	0
3	0
4	2 (10.0%)
5	17 (85.0%)
6	0
Total	20 (100.0%)

Types of seizures and SE

On the basis of type of seizure at onset, 90% (18) patients had motor convulsive seizure at onset and 2 (10%) patients had non motor seizures at onset (Table 8). Out of the 16 patients who presented with CSE in ER, 2 (10%) presented with focal SE, 7 (35%) patients presented with generalized onset SE, 6 (30%) patients had focal with bilateral tonic clonic SE, and only one (5%) had myoclonic seizure at onset presenting with myoclonic SE and 4 (20%) patients presented with NCSE. Out of these 16 patients with CSE, 13 patients converted into NCSE within initial 24 hours. Three patients continued to have CSE. Therefore, 17 patients finally had NCSE within 24 hours after admission (Table 8) and 3 (15%) emerged as SRSE.

Table 8: Type of SE and seizure at onset

	FOCAL	GENERALISED TONIC CLONIC	FOCAL WITH BILATERAL TONIC CLONIC	MYOCLONIC	NCSE
Type of seizures at onset	2	8	7	1	2
Type of SE at presentation to ER	2	7	6	1	4
Type of SE in first 24 hours after admission	1	1	1	0	17
CSE persisting beyond 24 hours	0	1	1	0	NA
NCSE persisting beyond 24 hours	NA	NA	NA	NA	15
CSE finally aborted after anaesthesia	2	7	6	0	NA
NCSE aborted after anaesthesia	NA	NA	NA	NA	15

Occurrence of antecedent seizures

On enquiring regarding past history of seizures, 4 (20%) of patients were found to have prior history of seizures and 80% had new onset SE. Out of these 4 patients with seizures in the past, 2 had focal onset with GTCS and one had complex partial seizures with secondary GTCS and one had GTCS (Figure 4). Of total 4 patients with prior seizures, 3 (75 %) had history of use of ASM in past.

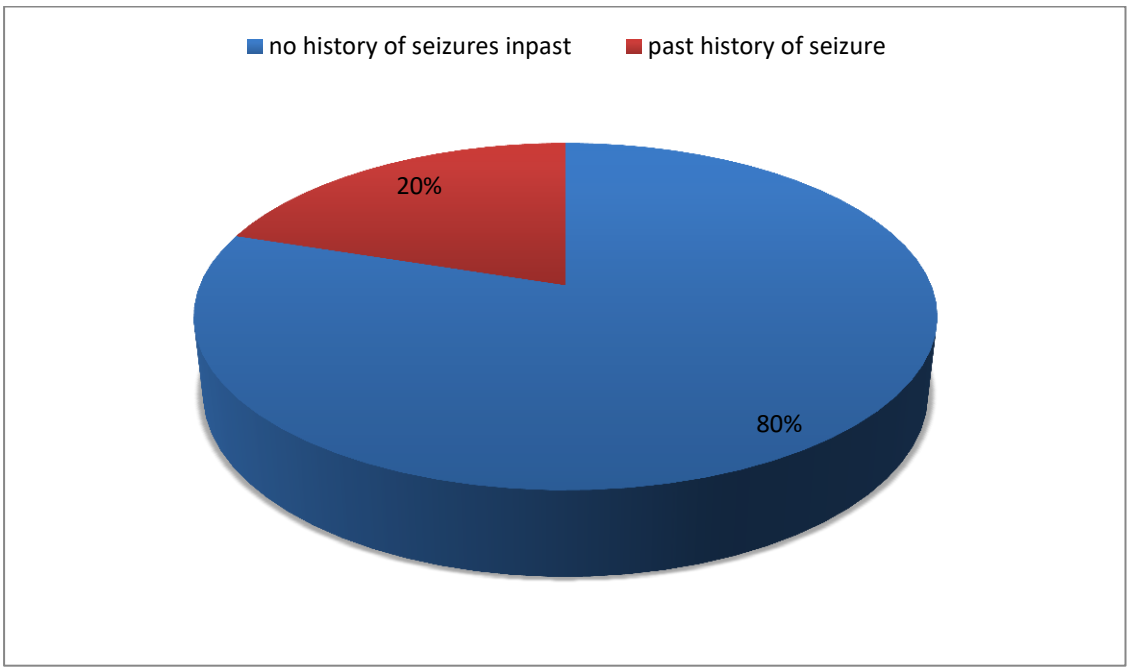


Figure 4: Distribution based on previous history of seizure

Treatment of RSE

The median dose of lorazepam (LZP) was 8 mg (range= 4-12), levetiracetam (LEV) 1500 mg (range = 600-1800), valproate (VPA) 1500 mg (range = 600-1800), phenytoin (PHT) 900 mg (range = 300-1000), and lacosamide (LCM) 400 mg (range=200-400) in patients with RSE. The third-line ASMs administered included midazolam in 13 (65%), LEV in 15 (75%), VPA in 4 (20%), and LCM in 1 (5%). Propofol was given for 3 patients, ketamine used in 2 patients along with ketogenic diet. Two patients required cycling of anaesthetic medications.

Frequency of cardiovascular comorbidities

The study included only those patients who lacked overt/ known cardiac disease. Among all the patients studied, only 4 (30%) patients were identified without any risk factors. Eight (40%) had history of hypertension, 20% were diagnosed with diabetes and 2 (10%) had both diabetes and hypertension. None had history of smoking or hyperlipidemia (Table 9).

Table 9: Distribution based on comorbidities

COMORBIDITIES	NUMBER OF PATIENTS N (%)
No risk factor	4 (20%)
HTN	8 (40%)
Diabetes mellitus +HTN	2 (10%)
Diabetes mellitus	4 (20%)
Smoking	5 (25%)
Hyperlipidemia	1 (5%)
Total	20 (100%)

Distribution based on etiology of RSE

In our study, the most common etiology was found to be CNS infection seen in 7 (35%) patients followed by autoimmune etiology in 4 (20%) patients, cerebral venous thrombosis (CVT) in 2 (10%) patients and toxin related was found as etiology in 2 (10%) patients (one patient each had alcohol intoxication and organophosphate poisoning). Relatively less common etiologies were trauma (5%), hypoxemic brain injury (5%), ischemic stroke (5%), and dural AV fistula (5%). (Table 10)

Table 10: Distribution of RSE based on etiology

ETIOLOGY	NUMBER OF PATIENTS N (%)
CNS infection	7 (35%)
Autoimmune	4 (20%)
Toxins	2 (10%)
Tumors	1 (5%)
CVT	2 (10%)
Trauma	1 (5%)
Hypoxemia	1 (5%)
Stroke	1 (5%)
DAVF	1 (5%)
Total	20

Electroencephalographic observations

Continuous EEG was done for all the patients. The state of consciousness when observed showed that out of 20 patients, 40% (8) were drowsy and 45% (9) were unconscious, 5% (1) was irritable, 10% (2) were drowsy and irritable at presentation. (Table 11)

Table 11: Distribution on basis of state of consciousness at presentation

CONSCIOUSNESS	NUMBER OF PATIENTS
Drowsy	8 (40.0%)
Drowsy +Irritable	2 (10%)
Irritable	1 (5%)
Unconscious	9 (45%)
Total	20

When distribution of background activity was evaluated in the EEG, delta range background most commonly observed in 9 (85%) followed by theta 3 (5%) and then suppressed background in 3 (5%). Three (15%) patients had delta with superimposed beta and one (5%) patient had delta with alpha coma. The further distribution of background pattern is given in the table below (Table 12). Twelve out of 14 patients with delta background, of which 10 patients had rhythmic and 4 had polymorphic delta.

Table 12: Distribution of EEG background

BACKGROUND	NUMBER OF PATIENTS N (%)
1-5 delta	9 (85.0%)
1-2 Hz delta + superimposed beta	3 (15.0%)
1-2 Hz delta+ spindle + alpha coma	1 (5.0%)
2-3 Hz delta + 4-5 Hz theta	1 (5.0%)
4-5 Hz theta	1 (5.0%)
4-6 Hz theta +superimposed beta	1 (5.0%)
8-9hz initially to 2-3 Hz	1 (5.0%)
Suppressed	3 (15.0%)
Total	20 (100.0%)

Pattern of epileptiform discharges

In terms of pattern of epileptiform discharges, the predominant pattern observed was generalized periodic discharges (GPDs) seen in 10 (50%) patients, of which 4 (20%) had only GPDs, 15% had GPDs with anterior predominance. Sporadic generalized discharges were seen in 20% patient, in which 3 patients had independent hemispheric discharges and one had focal predominance. (Table 13)

Table 13: Distribution of participants according to pattern of discharges on EEG

PATTERN OF DISCHARGES	NUMBER OF PATIENTS N (%)
Bilateral asynchronous hemispheric spike and wave	1 (5.0%)
GPDs	4 (20.0%)
Generalized frequent spike and wave with independent left hemispheric spikes	2 (10.0%)
Generalized spike and wave +independent frequent right hemispheric spikes	1 (5.0%)
Generalized frequent spike, polyspike, left temporal predominance	1 (5.0%)
GPDs, bifrontally predominant	3 (15.0%)
GPDs, right hemispheric predominant	3 (15.0%)
GPDs + LPDS (left>right post hemisphere)	1 (5.0%)
Left hemispheric abundant spike, polyspike	2 (5.0%)
Sporadic generalized sharp and spike bitemporal predominance + delta brush pattern	1 (5.0%)
Sporadic frequent spike and wave +spikes +polyspikes (bifrontal predominant)	1 (5.0%)
Total	20

Electrographic seizures were noticed in 12 (60%) patients during the first 24-hour recording. (Figure 5)

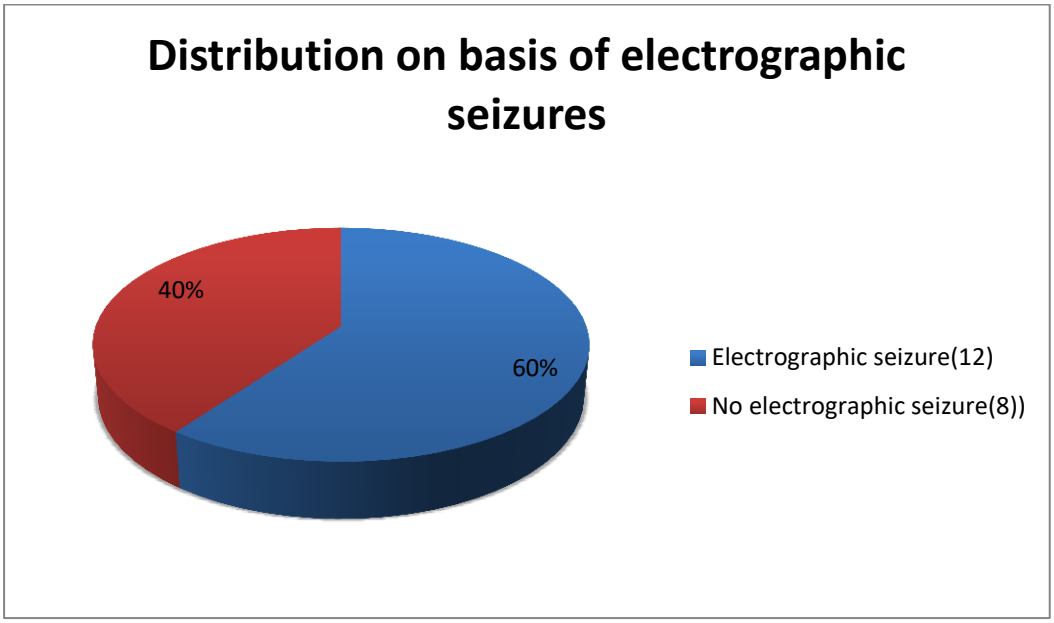


Figure 5: Distribution on basis of electrographic seizures

Using Salzberg criteria, NCSE cases were divided in 3 categories. Definite NCSE was noticed in 12 (60%) patients and possible NCSE in 5 (25%), no NCSE was observed in 3 (15%) patients. (Table 14)

Table 14: Distribution on basis of presence of NCSE

	NUMBER OF PATIENTS N (%)
Definite NCSE	12 (60.0%)
Possible NCSE	5 (35.0%)
No NCSE	3 (15.0%)

Burst suppression and inter burst intervals

Burst suppression pattern was achieved in 13 (65%) patients and in 7 (35%) no burst suppression was observed. Out of total 13 patients in which burst suppression was achieved, ≥ 10 sec burst suppression was achieved in 7 (35%) patients, and 5-9 sec burst suppression achieved in 3 (15%) patients. (Table 15)

Table 15: Frequency and characteristics of burst suppression on EEG

DURATION OF BURST SUPPRESSION	NUMBER OF PATIENTS N (%)
No burst suppression	7 (35.05%)
1-2sec burst suppression	1 (5.0%)
3-5 sec burst suppression	2 (10.0%)
5-9sec burst suppression	3 (15.0%)
>/=10 sec burst suppression	7 (35 .0%)
Total	20 (100.0%)

Cardiac Parameters

Cardiac injury and non-cardiac injury group

The patients were divided in two groups- **Group A**- Cardiac injury group and **Group B**- Non-cardiac injury group.

Cardiac injury group (Group A) included 18 (90%) patients, in which following parameters were included- LV and/ or RV dysfunction, inferior RWMA, T wave inversion, ST elevation, ST depression, QTc prolongation, raised Trop I and/or raised NT Pro BNP. (Figure 6).

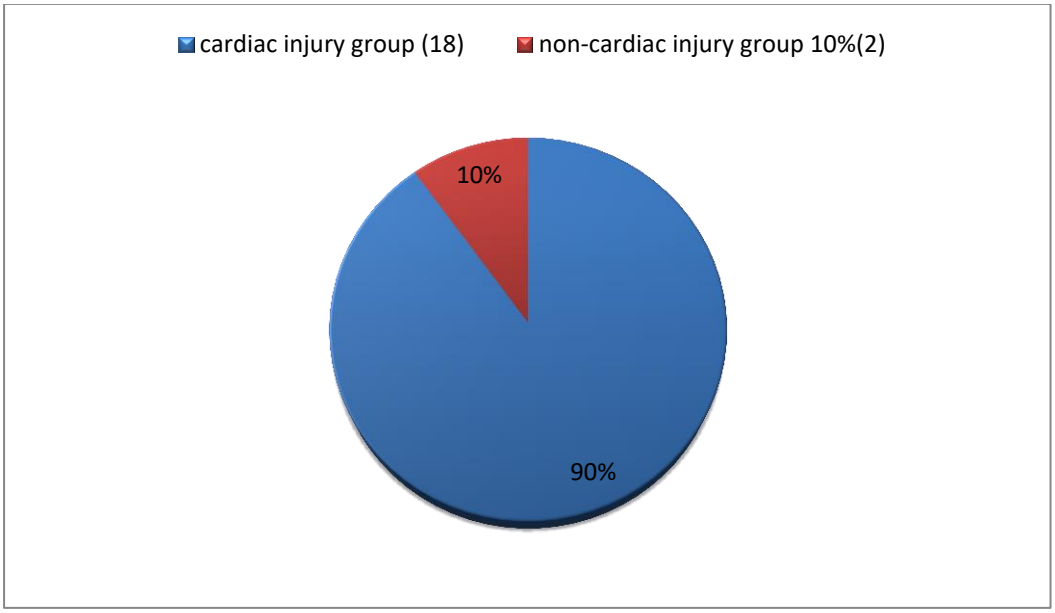


Figure 6: Distribution between cardiac injury and non-cardiac injury groups

Cardiac enzymes

Cardiac enzymes, both Trop I and NT pro BNP were monitored in all 20 patients. NT Pro- BNP was founded to be raised i.e more than 150 pg/ml in 12 (60%) patients and was in normal range in 6 (40 %). (Table 16)

Also, when Trop I monitored in this population, it was found to be raised in 13 (65%) patients and was in normal range in 7 (35 %) (Table 17)

Table 16: Distribution according to NT Pro BNP levels

LEVEL OF NT Pro BNP	NUMBER OF PATIENTS N (%)
Normal	8 (40.0%)
Raised >150pg/ml	12 (60.0%)
Total	20 (100.0%)

Table 17: Distribution according to Trop I levels

LEVEL OF TROP I	NUMBER OF PATIENTS N (%)
Normal	7 (35.0%)
Raised >0.5 mg/ml	13 (65.0%)
Total	20 (100.0%)

Holter findings

<u>Cardiac arrhythmias</u>

Cardiac arrhythmias occurred during the course of RSE in 9 patients (45%) and included sinus bradycardia (n = 4, 20%), AF (n = 2, 10.0%), V tach/VF (n = 2, 10.0%), and AV block (n = 1, 5%). (Table 18)

Table 18: Distribution of participants according to holter abnormalities

ABNORMALITIES ON HOLTER	NUMBER OF PATIENTS N (%)
V tach/VF	2 (10.0%)
AV block	1 (5.0%)
AF	2 (10.0%)
Sinus bradycardia	4 (20.0%)
Sinus tachycardia	20 (100.0%)
QTc prolongation	14 (70.0%)

QTc prolongation

QTc of more than 450 ms was taken are prolonged in males and more than 460 ms was taken as prolonged in females. QTc was prolonged in 70% (14) patients. (Table 18)

Heart rate changes

Sinus bradycardia occurred in 7 (35%) patients, and all patients 20 (100%) patients were found to have sinus tachycardia (>100 beats/minute). However, significant tachycardia (more than 150 /min) was observed in only 3(15%) patients. (Table 19)

Table 19: Distribution according to Heart rate

PARAMETER	NUMBER OF PATIENTS N(%)
HR <60 Beats/min	7 (35%)
HR >100 Beats/min	20 (100%)
HR >150 Beats/min	3 (15%)

Heart rate variability

HRV was studied over 24 hours and two variables were included- SDNN and RMSSD. SDNN more than 100 ms was taken as normal, seen in 2 (10%) patients. SDNN of 50-100msec was taken as ‘at risk patient’ and was found in 10 (50%) patients while less than 50 msec was considered abnormal and observed in 8 (40%) patients (Table 20).

Another heart rate variable observed was RMSSD, the value of 27±12msec being taken as normal. Eleven (55%) patients had normal and rest 45% had abnormal RMSSD. In patients with abnormal RMSSD, 35% had less than 15 msec RMSSD and 2(10%) patients had more than 39 msec RMSSD (Table 21).

Table 20: Distribution according to SDNN

VALUE OF SDNN	NUMBER OF PATIENTS N(%)
Less than 50 ms	8 (40%)
50-100 ms	10 (50%)
More than 100 ms	2 (10%)

Table 21: Distribution according to RMSSD

VALUE OF RMSSD	NUMBER OF PATIENTS N (%)
Less than 15 ms	7 (35%)
15-39 ms	11 (55%)
More than 39 ms	2 (10%)

2 D Echo findings

2D Echo done by the cardiologist in all 20 patients. Findings included normal LV and RV function in 16 (80%) ; generalized LV and RV dysfunction, which resolved on subsequent studies in 2 (10%); generalized LV dysfunction, which resolved on subsequent studies in 1 (5%); and 1 (5%) had inferior RWMAs and persistence of RWMAs on subsequent study. (Table 22)

Table 22: Distribution according to 2D Echo findings

ECHO FINDINGS	AT PRESENTATION (N=20)	AT DISCHARGE (N=10)
Normal LV and RV function	16 (80.0%)	9 (45%)
Generalized LV and RV dysfunction	2 (10.0%)	0 (0.0%)
Generalized LV dysfunction	1 (5%)	0 (0.0%)
Inferior RWMA	1 (5%)	1 (5%)
Total	20 (100.0%)	10 (100.0%)

Distribution of Cardiac injury parameters

Among the cardiac injury group, the most common observed abnormalities were in the cardiac enzymes. Trop I was raised in 13 (65%) patients and NT pro BNP was raised in 12 (60%) patients. QTc prolongation seen in 14 (70%) patients followed generalized LV and RV dysfunction in 2 (10.0%). Generalized LV dysfunction in one (5%), inferior RWMAs in one (5%), and ST changes were seen in one (5%) patient. (Table 23)

Table 23: Distribution of different parameters of cardiac injury group

PARAMETERS	CARDIAC INJURY N (%)
NT pro-BNP >150pg/ml	12 (60%)
Trop I >0.5 mg/ml	13 (65%)
Generalized LV and RV dysfunction,	2 (10.0%)
Generalized LV dysfunction	1(5%)
Inferior RWMA	1 (5%)
ST changes	1 (5%)
QTc prolongation	14 (70.0%)

Comparison of different cardiac parameters between cardiac injury and non-cardiac injury group

When compared between cardiac injury (Group A) and non-cardiac injury (Group B) group, RMSSD, AF and LV/ RV Dysfunction / Inferior RWMA, V tach / VF, and AV block were more deranged in cardiac injury group than non cardiac injury group and all were found to be statistically significant. **(**Table 24)

Table 24: Comparison of various parameters between cardiac injury and non-cardiac injury group

CARDIAC PARAMETER	GROUP A N=18		GROUP B N=2		P-VALUE
	Number	%	Number	%	
HRV					
SDNN	16	80%	2	10%	0.058
RMSSD	7	35%	2	10%	0.0561
Arrhythmia					
Sinus bradycardia	4	20%	0	0.0%	0.0035
V tach / V F	2	10%	0	0.0%	0.0028
AF	2	10%	0	0.0%	0.0035
AV block	1	10%	0	0.0%	0.0028
LV/RV Dysfunction/ Inferior RWMA	4	20%	0	0.0%	0.0035

Outcome

All the patients were admitted to the intensive care unit (ICU). Anesthetic agents were required in 13 (90%), and duration for which anesthetic agent was mean 11.09±17.9 days and median 4 (range 0-90) hours. Mechanical ventilation (MV) was required in all 20 patients. Mean length of hospital stay was 30.7 ± 22.07 days and median 27 days with range from 2-70 days. In-hospital mortality occurred in 10 cases (50%).

Change of functional outcome

At hospital discharge, functional outcome was poor (mRS 4-5) in 9 (45%). (Table 25) However, improvement occurred over time in subsequent 30 days for which follow-up data was available. Among survivors, follow-up data were available in 10 (50%) patients; conditions of 5 patients improved, 3 remained same, 2 patients declined and eventually died. Of the 5 patients who improved, 3 changed from poor to good functional outcome (mRS score of less than 3). (Table 25)

Table 25: Distribution of participants according to mRS

mRS	On admission N (%)	At discharge N (%)	During follow-up N (%)
1	1 (5%)	1 (5%)	1 (5%)
2	0	0	1 (5%)
3	0	0	2 (10%)
4	2 (10%)	4 (20%)	2 (10%)
5	17 (85%)	5 (25%)	2 (10%)
6	0	10	2 (10%)
TOTAL	20	20	10

On evaluating outcome in terms of GCS, 5% patients had GCS 1 at discharge which persisted as 1 on 30 days follow up, 3 (15%) patients had GCS 4-8 during discharge and one (5%) patient had GCS of 4-8 at 30 days follow up. Out of 10 survivors at discharge, 6 had GCS 9-15 at discharge and 7 had GCS 9-15 at 30 days follow up (Table 26).

Table 26: Distribution of participants according to GCS

GCS	On admission N (%)	At discharge N (%)	Final GCS at 30 days followup N (%)
3	4 (20%)	1 (5%)	0
4-8	9 (45%)	3 (15%)	1 (5%)
9-15	7 (35%)	6 (30%)	7 (35%)
Total	20	10	8

Mortality

In-hospital mortality was 50% (10 patients). Additional 2 patients died during the follow up period of 30 days. (Figure 7) Therefore final total mortality in RSE on 1-month follow-up was 60%.

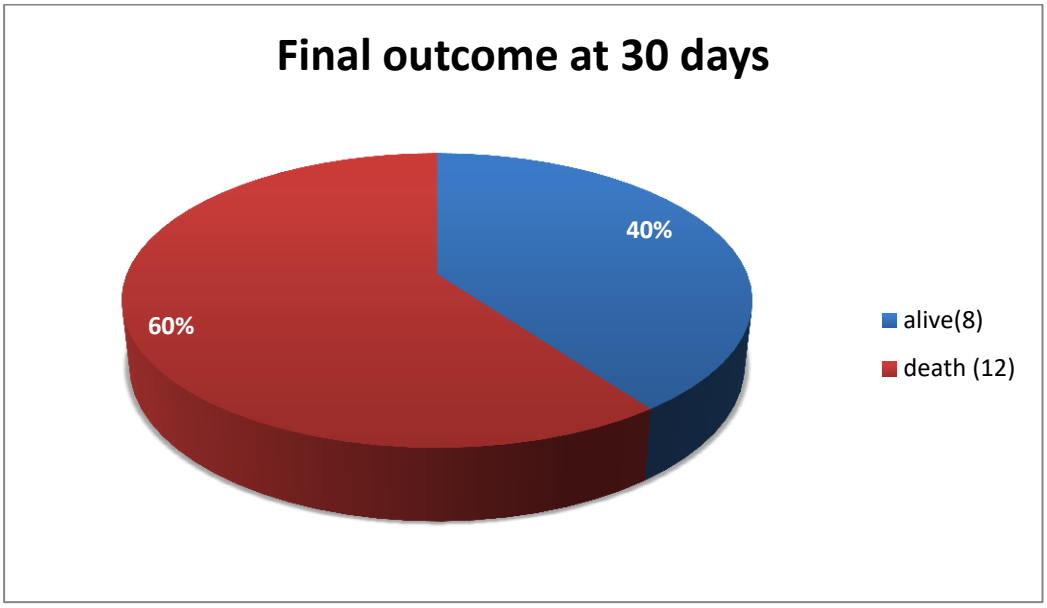


Figure 7: Distribution on the basis of final outcome at 30 days

Non-cardiac contributors to mortality

Association of age distribution with mortality

When mortality was reviewed at the end of hospital stay in terms of age distribution, out of 10 deaths, 50% population were ≤40 years and 50% were >40 years. Similarly, out of total 12 deaths at 30 days follow up, 50% of study group each were ≤40 and > 40 years, respectively. As such, no statistically significant association was found between age and mortality. (Table 27)

Association of gender with mortality

Comparing mortality at discharge and total mortality at 30 days follow up with gender, there is slight male predominance of deaths 60% of deaths at discharge and 58.3% at 30 days follow up), though this was not statistically significant (Table 27).

Association of etiology with mortality

The association of death at discharge was seen most commonly with autoimmune encephalitis (50%) followed by CNS infection (42.85%) and cerebrovascular diseases (33.33%). Similarly, higher frequency of death at 30 days follow up was observed with autoimmune encephalitis (75%) followed by CNS infection (42.85%) and cerebrovascular diseases (33.33%). However, this was not statistically significant (Table 27).

Association of comorbidities with mortality

The presence of comorbidities didn't effect mortality either at discharge or at followup. However, mortality was slightly higher in patients without comorbidities (75%) at discharge and at 30 days follow up (75%), though not statistically significant.

Association of GCS and mRS at presentation with mortality

Mortality was statistically significant higher in RSE patients with GCS ≤8 (69.23% and 79.6%, at discharge and at 30 days follow up, respectively) as compared with good GCS of >8 at presentation. (Table 27)

Mortality was statistically significantly higher in RSE patients with mRS >3 (52.63% and 63.15%, at discharge and at 30 days follow up respectively) as compared with good mRS ≤ 3 at presentation. (Table 27)

Association of EEG background activity with mortality

Mortality was 100% at 30 days follow up and 66.56% at discharge in patients of RSE with suppressed background. However, this observation was not statistically significant. On the other hand, patients with delta background activity were found to have mortality of 42.85% at discharge and 50% at 30 days but without statistically significant difference from those with theta or suppressed background. Mortality was 66.66% in patients with theta background, which remained same at 30 days follow up.

Association of burst suppression with mortality

Mortality at discharge and at 30 days follow up was higher in patients with burst suppression (58.33% at discharge and 75% at follow up) when compared with those with no burst suppression achieved, though it was not statistically significant. (Table 27)

Association of electrographic seizure with mortality

Patients having electrographic seizures were found to have mortality in 50% at discharge and 58.33% at follow up, although mortality was higher (62.5%) in those with no electrographic seizure at 30 days follow up. (Table 27) However, the difference was not statistically significant.

Association of periodic discharges with mortality

Patients with either generalized or lateralized periodic discharges was found to have mortality of 41.6% at discharge and 50% at 30 days follow up. On the other hand, 62.5% and 75% of patients with sporadic discharges died at discharge and at 30 days follow up, respectively. Though mortality at discharge and at follow up was higher in patients with sporadic discharges than those with periodic epileptiform discharges, the difference was not statistically significant.

Association of NCSE with mortality

In patients whose EEG showed persistence of NCSE despite cessation of clinical SE, mortality was 52.94% at discharge and 64.70 % at 30 days follow up. This was statistically significant both at discharge and follow up (P=0.001 and P=0.005, respectively). (Table 27)

Therefore, on studying the effect of different parameters including age, gender, etiology, comorbidities, GCS at presentation, mRS at presentation, EEG background, burst suppression pattern, electrographic seizures and NCSE with mortality at discharge and follow up, a few predictors of mortality were evident on univariate analysis. Poor GCS, poor mRS at presentation and NCSE were found to have significant correlation with mortality both at discharge and at 30 days post discharge. (Table 27)

Table 27: Distribution of non-cardiac parameters and their correlation with mortality

	Number of deaths at discharge N=10	P value	Total deaths at 30 days follow up N=12	P value
Age				
≤40 years(9)	5 (55.5%)	**1.000**	6 (66.67%)	**1.000**
>40 years(11)	5 (45.45%)		6 (54.54%)	
Gender				
Male(10)	6 (60%)	**0.656**	7 (70%)	**0.650**
Female(10)	4 (40%)		5 (50%)	
Etiology				
CNS infection (7)	3 (42.85%)	**0.500**	3 (42.85%)	**0.251**
Autoimmune (4)	2 (50.00%)	**1.000**	3 (75%)	**0.619**
Cerebrovascular (3)	1 (33.33%)	**0.474**	1 (33.33%)	**0.147**
Others (6)	5 (83.33%)	**0.350**	5 (83.33%)	**0.158**
Comorbidities				
No (4)	3 (75%)	**0.582**	3 (75%)	**0.619**
Yes (16)	7 (43.75%)		9 (56.25%)	
GCS at admission				
≤8 (13)	9 (69.23%)	**0.047 (S)**	10 (79.6%)	**0.032 (S)**
>8 (7)	1 (14.28%)		2 (28.56%)	
mRS at admission				
≤ 3 (1)	0(0)	**0.007 (S)**	**0(0)**	**0.007 (S)**
>3 (19)	10(52.63%)		**12(63.15%)**	
EEG background				
Delta (14)	6 (42.85%)	**0.628**	**7 (50%)**	**0.325**
Suppressed (3)	2 (66.66%)	**1.000**	**3 (100%)**	**0.242**
Theta (3)	2 (66.66%)	**1.000**	2 (66.6%)	**1.000**
Burst suppression				
Yes (12)	7 (58.33%)	**0.457**	**9 (75%)**	**0.356**
No (8)	3 (37.5%)		3 (37.5%)	
Electrographic seizure				
Yes (12)	6 (50%)	**0.890**	7 (58.3%)	**0.768**
No (8)	4 (50%)		5 (62.5%)	
NCSE				
Yes (17)	9 (52.94%)	**0.001 (S)**	11 (64.70%)	**0.005 (S)**
No (1)	1 (33.33%)		1 (33.3%)	
Epileptiform discharges				
Periodic discharges (12)	5 (41.6%)	**0.890**	6 (50%)	**0.670**
Sporadic discharges (8)	5 (62.50%)	**0.894**	6 (75%)	**0.576**

P ≤ 0.05 is significant

S- statistically significant

Association of cardiac parameters with mortality

The presence of markers of cardiac injury, cardiac arrhythmias or reduced HRV did not have any statistically significant difference on the mortality at discharge. (Table 28)

Table 28: Association of mortality at discharge with various cardiac abnormalities

Cardiac Abnormality	Patients alive at discharge N=10	Patients dying in hospital N=10	p-value
Presence of cardiac injury N=18 (%)	9 (50%)	9 (50%)	1.000
Presence of arrhythmia N=9 (%)	5 (55.55%)	4 (44.44%)	0.327
Presence of reduced HRV N=18 (%)	9 (50%)	9 (50%)	1.000

$P \leq 0.05$ is significant
S- statistically significant

However, out of all cardiac abnormalities during RSE, cardiac injury markers and HRV were a better prognostic marker of mortality at 30 days post discharge on univariate analysis (P= 0.032 each). (Table 29)

Table 29: Association of mortality at 30 days with various cardiac abnormalities

Cardiac Abnormality	Patients alive at follow up N=8	Total number of deaths N=12	p-value
Presence of cardiac injury N=18 (%)	7 (38.88%)	11 (61.11%)	0.032 **(S)**
Presence of arrhythmia N=9 (%)	3 (33.33%)	6 (66.66%)	0.670
Presence of reduced HRV N=18 (%)	7 (38.88%)	11 (61.11%)	0.032 **(S)**

$P \leq 0.05$ is significant
S- statistically significant

Final predictors of outcome of RSE by logistic regression

Out of the statistically significant parameters on univariate analysis, poor GCS (OR=8.55, $CI_{95\%}$=1.31-55.48, P=0.047) followed by presence of NCSE (OR=2.26, $CI_{95\%}$=0.51-10.03, P=0.007) followed by poor mRS (OR=2.00, $CI_{95\%}$=0.00-10.57, P=0.007) were found to have significance in predicting mortality at discharge. (Table 30)

Table 30: Final predictors of mortality in RSE at discharge

	ODDs RATIO	95%CI	P-VALUE
mRS ≥3	2.00	0.00-10.57	0.007 (S)
GCS ≤8	8.55	1.31-55.48	0.047 (S)
NCSE	2.26	0.51-10.03	0.007 (S)

Further, along with poor GCS, poor mRS at presenation and presence of NCSE, presence of cardiac injury and reduced HRV had poor outcome at 30 days post discharge. Among non cardiac variables, poor GCS (OR =7.32, $CI_{95\%}$=1.49-45.48, P=0.032) followed by presence of NCSE (OR =2.26, $CI_{95\%}$==0.51-10.03, P=0.007) and poor mRS (OR =2.26, $CI_{95\%}$=0.00-17.03, P=0.007) were found to be significant predictors of mortality at 30 days post discharge. Amongst cardiac variables, cardiac injury (OR =5.9, $CI_{95\%}$==1.4-24.3, P=0.032) followed by reduced HRV (OR =4.3, $CI_{95\%}$==2.6-21.3, P=0.032) were also found to be associated with poor outcome at 30 days post discharge

Table 31: Final predictors of mortality in RSE at 30 days

	ODDs RATIO	95%CI	P-VALUE
mRS ≥3	2.26	0.00-17.03	0.007 (S)
GCS ≤8	7.32	1.49-45.48	0.032 (S)
NCSE	2.26	0.51-10.03	0.007 (S)
CARDIAC INJURY	5.9	1.4-24.3	0.032 (S)
REDUCED HRV	4.3	2.6-21.3	0.032 (S)

DISCUSSION

This study was carried out in All India Institute of Medical Sciences, Jodhpur, Rajasthan over 18 months from January 2021 to June 2022 with major part of the data collection falling during the period of SARS COVID-19 global pandemic. The study focused on evaluating cardiac abnormalities in RSE and their relation to functional outcome. We studied the ECG/ Holter, 2D Echo, Trop I and NT pro BNP changes in RSE patients in first day after admission, at discharge or death and 30 days later. Across the world literature, RSE has been studied widely both in the western world and Asian continent. For the present study, all 20 patients presenting with RSE that fulfilled the inclusion criteria were recruited and outcome in terms of MRS, GCS at end of hospital stay, and 30 days after discharge was observed in the two cohorts of those with cardiac injury and no cardiac injury.

PATIENT DEMOGRAPHICS

Gender distribution among these patients showed equal female to male ratio of 1:1. A 9- year cohort study by Delaj et al retrospectively assessing prevalence and related clinical profile of adult patients with RSE and showed female to male ratio in RSE was1: 1.57. [28] Sinha et al observed female to male ratio of 1:1.13 in 98 patients of RSE, which was similar to our findings. [66] On the contrary Dubey et al showed a male predominance with female to male ratio of 1:2.25 in 81 patients. [69]

The age wise distribution showed that the third and fourth decade was the most common presenting age of RSE in our study with mean age of presentation was 47.75±17.2 years and median age was 46 (range 22-80) years. This finding correlated with other studies in which age of presentation for RSE ranged from 21-97 years. Stephan et al studying 73 patients of RSE showed mean age of presentation as 63 years. [2] Another study by Fersili et al consisting of 776 patients from around the world, showed a mean age of presentation as 39.8 ± 25.9 (range 0-92) years. In the same study, when data was compared on regional basis, patients from Asia were significantly younger than those from Europe and the

Americas with mean age of 22.4, 48.2, and 40.5 years respectively (P < 0.001). [20] This finding of patients of relatively younger age of presentation in Asian population was also reflected in our study. Additionally other Indian studies have also shown early onset of RSE in the Indian population compared to other parts of the world. Dubey et al showed median age of 38 years in 35 patients and study by Jayalakshmi et al showed a mean age of 30.7 ± 18.8 years in 42 patients of RSE. [69,70] Contrary to this Sinha et al showed a median age of 13 years in 98 patients. [71]

The literacy rate in our study was 60%, of which 50% had studied up to high school. Socio economic class analysis revealed that 60% of the patients belonged to lower and upper lower class while only 20% belonged to lower middle class. None of the patients belonged to upper or upper middle class according to modified Kuppuswamy classification of socioeconomic status. Till now, no available study has correlated socio economic status with RSE.

Onset to admission time

The mean time within which patients in our study got admitted to ER after onset of seizure was 8.80±7.024 hours, which is way longer than the available literature. Mayer et al reported mean interval between onset of seizure and arrival to ER was 1.3 ±0.9 hours. [15]

In the Indian context, Sinha et al reported median of 2 hours (range 3.5±2 hours) as duration of SE before NICU admission while in other study by Dubey et al reported median time duration before starting treatment of 2 hours and range 0.17-160 hours. [69,71]

Amongst our cohort the median interval from onset of seizure to ER admission was 6.50 hours (range- 1-48) hours. Though we have not looked into specific factors of this delay the possible reasons may be multifactorial. As the catchment area of the institute is wide with low population density, increased travel time from the villages would have contributed significantly to the delay. Additionally, the scarcity of hospitals in rural areas, the lack of specialists in peripheral hospitals and

delayed recognition of symptoms both by relatives and health personnel along with local customs and beliefs may have contributed to the same.

GCS at presentation

In our study we found out that 65% patients had poor GCS (GCS ≤ 8) while 35% patients had good GCS (9-15) at the time of presentation. Considering the level of consciousness as predictor of treatment responsiveness at SE onset, Giovannini et al found that 42% of RSE had stuporous/ comatose presentation (GCS ≤ 7) compared to only 10% who were treatment responsive (p value < 0.005). [72] This was similar to our cohort with a greater fraction having poor GCS, suggesting a direct correlation with evolution of SE to RSE.

mRS at admission

At admission, we observed that majority (95%) patients had mRS 4-5. This implies greater severity of deficit of patients of RSE at time of admission as only one patient had mRS of 1. In comparison, Hocker et al observed mRS of 5 in 4(6.5%), mRS 4 in 8(12.9%), mRS 3 in 15 (24.2%), mRS 2 in 10 (16.1%), mRS 1 in 11 (17.7%) and mRS 0 in 14(22.6%). [73] This implies that majority of patients in our cohort came in with SE having prolonged generalized seizures with persistence of unconsciousness at presentation.

Type of seizures and SE

On the basis of type of seizure at onset, 90% patients had motor seizure at onset and 75% patients had generalised SE (Table 17). However, 4 (20%) patients presented with NCSE to ER. Interestingly 83.33% (15 of 18 patients) converted from CSE to NCSE within 24 hours. In most studies of SE, the commonest subtype reported has been generalized SE. Delaj et al observed generalized SE as the most frequent type seen in 41.05%, followed by complex partial seizures in 36.6% and simple partial seizure in 14.9%. NCSE in coma was observed in 7.1% of RSE [28]. In the study by Mayer et al, generalized CSE was found in 73% and NCSE in 23% [2]. Likewise Rossetti et al observed simple partial SE in 4.1%, complex partial seizure in 43.75%, generalized CSE in 46.87% and NCSE with coma in 5.2% [53].

On the contrary in an Italian study, 63% cases had NCSE, 25% cases with partial convulsive status, 10.8% with generalized convulsive status, and 1.2% with myoclonic status epilepticus. [72]

When regional difference for type of RSE was studied, Asian patients were found to present with CSE more frequently than NCSE compared to those from Europe and the Americas (71%, 53%, and 44%, P <0.001). However in the total group, SE was convulsive in 55%, non convulsive in 19%, convulsive evolving to non-convulsive in 21%, and of other semiology (epilepsia partialis continua, absence status, other) in 4%. [56]

Past history of seizure/epilepsy

In our study population, majority 80% had new onset SE while remaining had prior seizures. This is similar to other studies. [70,72] Giovannini et al found history of epilepsy before the SE development in 28% while it was 35% in study done by Jayalakshmi et al. [70,72]. Similarly, 63% had no prior history of seizure or epilepsy in the study done by Fersili et al. [56] Among cryptogenic RSE patients, 39% had a positive history of epilepsy, 59.5% had new onset RSE, and 2% history of epilepsy was uncertain. On the other hand, Hocker et al reported a higher frequency of prior seizures. [73] Previous history of seizure was present in 59.7% and previous history of SE in 27.9%. However, history of epilepsy, previous SE, or type of SE did not influence the outcome.

Treatment of RSE

In our study, ASMs administered were LZP, LEV, VPA, PHT, and lacosamide. LZP administered in 100%, midazolam in 65%, PHT in 50%, LEV in 75%, VPA in 20%, and lacosamide in 5%. RSE was controlled in 90% patients after administration of the third-line ASM. Anesthetic agents were given in a few patients; propofol 15% , ketamine 10% patients, two of the patients required cycling of ASM. Our study reflects a recent trend towards high usage of LEV in SE. This is in contrast to study by Hocker et al, in which first- and second-line drugs of choice were most commonly LZP (60%) and fosphenytoin sodium (52%),

respectively. The most commonly used anesthetic agent was midazolam (n=38), followed by propofol (n = 33), pentobarbital (n = 16), isoflurane (n = 3), ketamine (n = 3), and lidocaine (n = 1). [73]

Cardiovascular Comorbidities

Cardiovascular comorbidities were noted in 70% of our patients, which reflects their probable contribution towards morbidity and mortality. Dubey et al showed that RSE patients had multiple comorbidities in 31.4 %, hypertension in 42.9% and diabetes in 20% [69]. Similarly, Mayer et al found that the most common comorbid conditions associated with RSE were hypertension 39%, epilepsy 38%, stroke 28%, diabetes mellitus 28%, and coronary artery disease 22%. [2]

Etiology

We observed the most common etiology of RSE was CNS infection (35%) followed by autoimmune encephalitis (20%) and cerebrovascular disease (20%). Also, majority (85%) had acute symptomatic seizures this is much higher than by Delaj et al where acute symptomatic seizures in 58.6%, followed by progressive symptomatic in 20.9%. Acute inflammatory etiology (infectious or autoimmune), was found in 8% RSE and 18% SRSE. [28] Similarly, as per Giovannini et al, acute symptomatic etiology was found in 64%, remote symptomatic etiology in 12%, progressive symptomatic etiology in 16%, and multifactorial etiology in 6%. The frequency of acute symptomatic SE was higher in RSE/super-RSE than in responsive SE (77% versus 56%, respectively. [72] In another cohort of 45 patients by Vooturi et al, out of 58.6% with acute symptomatic etiology CNS infections accounted for 31%. [74] Significantly higher percentage of patients with RSE had an etiology of CNS infections than nonresponsive SE group (44.4% vs. 23.5%; P = 0.0171). On further analysis, amongst the CNS infections, the incidence of viral encephalitis was significantly higher in RSE than in non-responsive SE (31% vs. 6.2%; P = 0.0004).

Jayalakshmi et al also found acute symptomatic etiology in 69% of which presumed encephalitis was more common in RSE (39%). CNS vascular etiology

was noted in 14.2% of RSE. Elderly patients had significantly higher incidence of metabolic and vascular etiology compared to adults and children. [70] Dubey et al showed RSE was associated with CNS infections in 34.3% (encephalitis in 5, meningitis in 6, neurocysticercosis in 1); metabolic aetiologies in 37.1%; renal failure in 9, 8 of whom were dialysis-dependent; liver failure in 1; hyponatremia in 1; prolonged hypoglycemia in 1; hyperglycemic hyperosmolar state in 1; stroke in 5 (14.3%) (venous in 1, arterial ischemic in 2 and intracerebral haemorrhage in 2); drug withdrawal in 1 (2.9%); and miscellaneous causes in 3 (8.6%). [69]

On comparing regional difference for etiology of RSE, Fersili et al noticed infections as frequently reported etiology in Asian (30%), whereas it was only 15.4% in the Americas and 12.3% in Europe. In particular, the incidence of acute encephalitis was significantly higher in Asia (n = 41, 20.9%) than in Europe (n = 26, 5.7%) or the Americas (n = 7, 4.7%, $P < 0.01$). Vascular etiologies were more frequent in Europe (n = 75, 16.6%) than in Asia (n = 11, 5.6%, $P < 0.01$). There was a non-significant trend toward a higher incidence of traumatic etiologies in Europe (n = 28, 6.2%) and the Americas (n = 7, 4.7%) than in Asia (n = 1, 0.5%). [56]

EEG features in RSE

Majority patients showed background of delta on EEG in 85% followed by theta (5%) and then suppressed background in 5%. GPDs were the most common epileptiform pattern seen in 50% while sporadic discharges were seen in 20% and electrographic seizures in 60%.

Background slowing is the commonest EEG abnormality in RSE followed by periodic discharges. Mayer et al observed that diffuse slowing was seen in 50%, focal slowing in 23%, interictal spikes or sharp waves seen in 38%, PLEDs in 42% and electrographic seizures in 42% of 26 patients of RSE. [2] Although interictal epileptiform activity and electrographic seizures occurred more frequently after RSE, only PLEDs were significantly associated with RSE.

Sinha et al showed that EEG was normal in 18.4% and abnormal in 81.6%. Diffuse

slowing of background activity was seen in 36.84%, generalized epileptiform discharges in 50%; focal epileptiform discharges in 7.8%; continuous ictal discharges in 5.26%; multifocal epileptiform discharges in 5.26%; burst suppression discharges in 2 and PLEDs in 5.26%. [71] Similarly, EEG during the first 24 hours showed ictal discharges in 43% SE patients, periodic patterns in 12% and postictal slowing and/or interictal epileptiform activity in 45%. [55]

The burst suppression pattern is often used to monitor the status of RSE and response to anesthetic medications. This was achieved in 65% patients in our study. Burst suppression was achieved in 12% patients of RSE in study done by Dubey et al. [69] Hocker et al retrospectively showed that 50% of RSE had burst suppression. [73]

Cardiac injury in RSE

Markers of cardiac injury were found in 90% patients. This finding is relatively higher than study by Hocker et al wherein 62.9 % patients demonstrated markers of cardiac injury. [5] Among the cardiac injury group in our study, the most common observed abnormalities were in the cardiac enzymes. Raised cardiac enzymes, either one or both suggesting cardiac injury, were positive in 90% of RSE. Trop – I was raised independently in 65% patients and NT pro BNP in 60% patients. On the other hand, troponin levels drawn at onset of SE were elevated in nine (39.1%), with a mean level of 0.09+/- 0.2 ng/ml in a previous study (normal <0.01 ng/ml). [5] The frequency of patients with raised NT pro BNP in RSE as seen in our patients was higher than the study done in drug resistant epilepsy by Faria et al where 23% patients showed raised NT pro BNP within 12- 18 hours of seizure onset. [79]

ST changes

ST changes were rare in RSE (only 5%) in our study. This is contrary to other studies where ECG recordings obtained at onset of SE in 35 patients showed ST elevation in a regional distribution in 11.4%, ST depression in 5.7%, T-wave inversion in 37.1%, nonspecific ST changes in 37.1%, and normal or no new

abnormality 34.3%. [5] In another study by Zijlams et al in 81 patients with intractable epilepsy, ST elevation/depression was found in 3.7%, and T wave inversion 9.8%. [75] In a study done by Nei et al, ST elevation was found in 3 (7.3%). [76]

QTc prolongation

QTc prolongation was consistently noted in 70% of our patients and was the most common marker of cardiac injury. As per study by Hocker S et al, QTc was prolonged in eight patients (22.9%). [11] QTc was increased in RSE patients associated with ventricular arrhythmias (520.3 ± 87.3 msec) compared with those without ventricular arrhythmias (455.9 ± 74.1 msec). However, no QTc interval changes were noted in 43 refractory epilepsy patients during partial seizures in another study. [76]

Cardiac arrhythmias

Cardiac arrhythmias occurred during the course of RSE in 9 patients (45%) in our study cohort. Though sinus tachycardia (>100 beats per minute) was present in 100% of RSE, significant tachycardia (>150 beats per minute) was present in 15% and only these were included as cardiac arrhythmia in our study. Compared to this, cardiac arrhythmias occurred in SE in 91.4% in study done by Hocker et al and included sinus tachycardia (65.7%), sinus bradycardia (48.6%), AF/AFL (20.0%), V Tach/VF (11.4%), and AV block (5.1%). Intervention for the arrhythmia was required in 14 cases (40%). [11] Dubey et al found that cardiac arrhythmias occurred in 2.9% [69]. In another study cardiac arrhythmias occurred in 35% and required intervention in 66.67%; the need for intervention correlated with poor functional outcome (P = 0.01). One patient experienced a non-ST- segment elevation myocardial infarction. [72] Compared to SE, in patients with intractable epilepsy there is a predilection for symptomatic arrhythmias.

Zijlams et al observed sinus tachycardia (n = 62, 76%), sinus bradycardia (n = 11, 13.5%), and AV block (n = 2, 2.4%) in patients with intractable epilepsy. Further, heart rate of more than 150 beats /min was found in 13 (16%). [75] Similarly in

study done by Nei et al, 23 (53%) patients had sinus tachycardia (heart rate more than 100 beats/ min) during the ictal or postictal period, bundle branch block in 3 (6.2%) and AF in one (2.0%). [76]

Echocardiographic abnormalities

In our study group, normal LV and RV function was noted in 80% while generalized LV and RV dysfunction in 10%, generalized LV dysfunction and RWMAs in 5% each were detected. This was remarkably similar to the study done by Hocker et al, in which 70% had normal LV and RV function; 14% had generalized LV and RV dysfunction, which resolved on subsequent studies; 7.1% had generalized LV dysfunction, which resolved on subsequent studies; and 7.1% had RWMAs [11]

Heart rate variability

HRV was studied in our study using 2 variables, SDNN and RMSSD. SDNN of 50-100msec was taken as 'at risk patient' and was found in 50% while less than 50 msec considered abnormal was observed in 40% patients. (67) Hence total of 90% did not have normal SDNN. Laniger et al retrospectively reviewed heart rate data including R-R intervals and SDNN in 53 adult patients with SE. [63] There was a statistically significant difference between the patients with non-status EEGs with average SDNN versus with SE. The decreased SDNN was suggestive of decreased HRV seen in the SE group.

Course in hospital and outcome

In our study all patients required MV during the period of RSE with mean length of hospital study of 30.7±22.016 days (median duration- 27; range 2-70 days). MV was required for the management of RSE because most of the intravenous ASMs used in treatment result in respiratory suppression or hypotension, or both especially in those who evolved to SRSE (15%). Final cumulative mortality in our patients at 30 days after discharge was 60% of which majority 50% patients died at the end of hospital stay.

In the study by Delaj et al, MV was required in only 16% RSE patients whereas it was necessary in 90.48% with mean length of hospital stay of 27.7±37.3 days in the study done by Hocker et al. [11, 28] On the other hand, in a cohort of 45 patients of RSE by Vooturi et al, the median survival time of RSE patients in NICU was 9.59 days. [74] All the patients with RSE required MV, which corroborated with our study result. The duration on ventilator in RSE patients was 6.9 ± 9.0 days. [74] Similarly, Ferlisi et al noted mean duration of ICU stay of 18.41 ± 22.8 days. [56] ICU duration was longer in patients from Asian (mean= 22.8±24.1 days) than from Europe (16.3±18.9 days, $P < 0.05$) or from the Americas (19.31±26.3 days). This was contrary to the study done by Jayalakshmi et al in which the mean duration of MV was 3.4±1.3 days in RSE group. [70] However, in another Indian study, the median length of hospital stay of the patients was 15 days (range=1-79). [69] Dubey et al observed that 65.7% of patients with RSE required MV with mean duration of 7.43±.43t days and 40% of RSE requiring MV died in the hospital, suggesting that patients requiring MV had poor outcome (p = 0.05). [69]

Predictors of Mortality in RSE

In our cohort of patients with RSE, none of the demographic variables such as age, gender, socioeconomic status or cardiovascular comorbidities had any significant association with mortality. Dubey et al had shown that age above 60 years (OR = 1.95, $CI_{95\%}$ = 0.10-4.66, p = 0.02) had poor outcome. [69] Similarly, 60% of the mortality were in those of age ≥ 65 years in study by Rosetti et al. [23] We noted a slight male predominance (60% of deaths at discharge and 58.3% at 30 days follow up), in another study by Rosetti et al mortality was higher in male population (60%).[23] On the contrary, Sinha et al noted that males with RSE have lesser mortality (47%). [71]

In our study, RSE due to autoimmune encephalitis, followed by CNS infection and cerebro-vascular conditions had higher mortality discharge and at follow up. However, it did not emerge as predictor of mortality on univariate analysis. Among Indian patients, Jayalakshmi et al noted mortality in 35.7% RSE with higher

percentage of deaths in patients with presumed encephalitis than other etiologies (39.1% vs. 12.2%; p = 0.001). [70] Acute symptomatic etiology accounted for 85·3% of the deaths in the entire cohort (p = 0.001) when compared to all other etiologies. Among acute symptomatic etiology presumed encephalitis was the major cause of death accounting for 52.9%. On the other hand, Dubey D et al found metabolic etiology (OR = 3.85, $CI_{95\%}$ = 0.241-61.6, p = 0.05) was predictor of poor outcome. [69]

Clinical status at presentation as predictor

In our study mortality was statistically significantly higher in RSE patients presenting with poor GCS ≤8 and poor mRS >3 when studied at discharge (69.23% and 53.63%, respectively) as well as total deaths at 30 days follow up (79.6% and 63.15%, respectively).

In a study done by Giovannini et al, in-hospital mortality was significantly higher, 42% in patients of RSE presenting with GCS ≤ 7 [72]. Hocker et al reported 31.9% RSE presented with mRS ≥4 at admission and in-hospital mortality as 31.75%, though correlation between mortality and poor mRS was not studied. [73]

EEG descriptors as predictors of mortality

Patients with suppressed background had more mortality at discharge and at 30 days (66.66%) and (100%) respectively but there was no statistically significant difference from those with delta or theta background though all patients with suppressed background died at 30 days follow up. Sinha et al observed that mortality was 21.5% in patients with abnormal EEG. [71]

Likewise, burst suppression pattern was noted in our cohort in 58.33% of deaths at discharge and 75% of total deaths at follow up, though not statistically significant. Dubey et al also showed that EEG burst suppression was associated with poor outcome. [69] In another study by Hocker et al, 81.48% of RSE with burst suppression had poor functional outcome. [73] On the other hand, seizure control without burst suppression (3.7%) correlated with a good functional outcome at hospital discharge (P = 0.01) [73]

Similarly, the presence of electrographic seizures in the first 24 hours did not show any statistically significant effect on mortality at discharge or follow up which was counter-intuitive. This finding is opposite to the study by Triem et al showing persistent electrographic seizures in 15% of treated patients after the cessation of clinical SE was associated with poor prognosis. [79]

On the other hand, the presence of NCSE on EEG even after clinical cessation of convulsive SE was noted in 52.94% and 64.70% of deaths at discharge and at follow up. This was a statistically significant predictor of mortality both at discharge and follow up (P=0.001 and P=0.005, respectively). This is in line with similar results where mortality was as high as 86% in patients with NCSE. [55]

Cardiac parameters as predictors of mortality

Our study demonstrated a statistically significant association between cardiac injury and mortality at 30 days follow up, though not in the in-hospital period. In a study on RSE with hospital mortality of 34.3%, the cardiac injury group comprised 45.5% while it was 15.4% in patients without markers of cardiac injury. [2] Though the mortality was higher in the group with markers of cardiac injury, it was not significant ($p = 0.14$). In a study done by Ibrahim et al, the overall mortality rate was higher among patients of CSE with cardiac injury (13.9%) than among those without cardiac injury (2.6%), confirming the role of cardiovascular complications as a cause of death in patients with CSE. [80] Kurukumbi et al reported that all deaths due to CSE had ECG abnormalities. [59]

In our study, mortality was higher in patients with reduced HRV and it showed significant correlation in terms of mortality at 30 days follow up. Laniger et al retrospectively reviewed heart rate data including R-R intervals and SDNN in 53 adult patients with SE. [63] There was a statistically significant difference in SDNN between patients with non-status EEGs and SE groups. The decreased SDNN was suggestive of decreased HRV seen in the SE group.

Final predictors of mortality

All the factors that emerged significant on univariate analysis, also contributed as predictors of mortality after logistic regression. Therefore, in our study the predictors of mortality at discharge were poor GCS, poor mRS and presence on NCSE. Along with these three parameters, presence of markers of cardiac injury and reduced HRV predicted poor outcome at 30 days post discharge.

In study done by Vooturi et al, in logistic regression analysis, out of independent variables (acute symptomatic etiology, viral encephalitis, fever, septicemia, hepatic failure, renal failure, HIE and acidosis) was statistically significant ($P < 0.0001$), the only predictor of death was fever with an odds ratio of 8.55 ($P = 0.024$) [74]. In another study by Sinha et al prolonged duration of NICU stay and prolonged ventilator requirement were significantly related to poor outcome. [71] Similarly Dubey et al, after multivariate analysis showed, the predictors of RSE were unfavourable STESS (OR=2.2, $CI_{95\%}$=1-36.33, p=0.05) and duration of SE before treatment (OR = 3.35, $CI_{95\%}$ = 0.243-0.779, p = 0.01)[69]. Hocker et al found that patients with cardiac arrhythmia requiring intervention had poor outcome but after comparing with other parameters it was concluded that though cardio pulmonary complications were common and increased the risk of mortality and poor functional recovery, outcome was primarily dependent on the success or failure of aborting the seizures [73]

CONCLUSION

This study found that markers of cardiac injury are frequent in RSE and abnormalities of cardiac enzymes followed by QTc prolongation were the most common in our study. Along with these cardiac markers, HRV correlated with poor outcome in our study.

In addition to poor clinical status in the form of GCS ≤ 8 and mRS >3, andpersistence of NCSE, these cardiac markers and HRV are important poor prognostic markers with high odds for mortality in RSE.

Routine analysis of ECG, 2D Echo, holter and cardiac enzymes like NT –Pro BNP, Trop I as affordable and easily accessible, non-invasive tools to observe cardiac abnormalities in RSE patients is recommended.

Future research should study patients with RSE prospectively using a standardized protocol of cardiac evaluation so as to gather sufficient information to evaluate the pathophysiology of cardiac changes in these patients.

LIMITATIONS

- The primary limitation of this study is the small sample size of the study. Only 20 patients could be included in the study as the period of recruitment collided with the global pandemic of COVID-19 pneumonia. Our center being a dedicated COVID care facility, less number of patients visited for acute illness and so we could recruit less patients. Also follow up was difficult. For more comprehensive review of cardiac involvement in RSE, large sample size is required. Also, studies are not so easy to be carried out in RSE though one should aim to have a large sample size with more varied presentation.

- Our cohort of RSE had low GCS due to NCSE. Thus almost 50% required anaesthetic agents and effect of these anaesthetic agents on cardiovascular system might have confounded the results.

- All the patients were followed up at discharge and at 30 days. However, more prolonged follow up is required to assess the further evolution of long-term cardiac changes in RSE.

REFERENCES

1. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015 Oct;56(10):1515-23.
2. Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Archives of neurology. 2002 Feb 1;59(2):205-10
3. Chang CJ, Chang HW, Chang WN, Huang LT, Huang SC, Chang YC, Hung PL, Chang CS, Chuang YC, Huang CR, Tsai NW. Seizures complicating infantile and childhood bacterial meningitis. Pediatric neurology. 2004 Sep 1;31(3):165-71
4. Marawar R, Basha M, Mahulikar A, Desai A, Suchdev K, Shah A. Updates in refractory status epilepticus. Critical Care Research and Practice. 2018 Oct;2018.
5. Knake S, Rosenow F, Vescovi M, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 2001;42(6):714–718
6. Devinsky O, Bundock E, Hesdorffer D, Donner E, Moseley B, Cihan E, Hussain F, Friedman D. Resolving ambiguities in SUDEP classification. Epilepsia. 2018 Jun;59(6):1220-33.
7. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: a nationwide population-based cohort study. Neurology. 2017 Jul 11;89(2):170-7
8. Goldman AM. Mechanisms of sudden unexplained death in epilepsy. Current opinion in neurology. 2015 Apr;28(2):166.
9. Assis TM, Bacellar A, Costa G, Nascimento OJ. Mortality predictors of epilepsy and epileptic seizures among hospitalized elderly. Arquivos de Neuro-psiquiatria. 2015;73:510-5.
10. Hawkes MA, Hocker SE. Systemic complications following status epilepticus. Current neurology and neuroscience reports. 2018 Feb;18(2):1-9

11. Hocker S, Prasad A, Rabinstein AA. Cardiac injury in refractory status epilepticus. Epilepsia. 2013 Mar;54(3):518-22
12. Lotufo PA, Valiengo L, Bensenor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia. 2012 Feb;53(2):272-82
13. Baysal-Kirac L, Serbest NG, Şahin E, Dede HÖ, Gürses C, Gökyiğit A, Bebek N, Bilge AK, Baykan B. Analysis of heart rate variability and risk factors for SUDEP in patients with drug-resistant epilepsy. Epilepsy & Behavior. 2017 Jun 1;71:60-4
14. Surges R. The many facets of cardiac complications in epilepsy. Journal of Neurosciences in Rural Practice. 2014 Jan;5(01):6-7
15. Horváth L, Fekete I, Molnár M, Válóczy R, Márton S, Fekete K. The outcome of status epilepticus and long-term follow-up. Frontiers in Neurology. 2019 Apr 26;10:427.
16. Timkao S, Pranboon S, Thepsuthammarat K, Sawanyawisuth K. Incidences and outcomes of status epilepticus: a 9-year longitudinal study. Epilepsy Behav. 2015;49:135-7
17. Szczurkowska PJ, Polonis K, Becari C, Hoffmann M, Narkiewicz K, Chrostowska M. Epilepsy and hypertension: the possible link for SUDEP. Cardiol J. 2019 Sep 30
18. Van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. Journal of Neurology, Neurosurgery & Psychiatry. 2016 Jan 1;87(1):69-74
19. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. Journal of Neurology, Neurosurgery & Psychiatry. 2005 Apr 1;76(4):534-9.
20. Ferlisi M, Hocker S, Trinka E, Shorvon S, International Steering Committee of the StEp Audit, Singh G, Kalviainen R, Kramer U, Godoy D, Newton C, O'Brien T. Etiologies and characteristics of refractory status epilepticus cases in different areas of the world: Results from a global audit. Epilepsia. 2018 Oct;59:100-7.

21. Bassin S, Smith TL, Bleck TP. Clinical review: status epilepticus. Critical Care. 2002 Apr;6(2):1-6
22. Kohli S, Pasangulapati SB, Yoganathan S, Rynjah GL, Prabhakar AT, Aaron S, Alexander M, Mathew V. Study of refractory status epilepticus from a tertiary care center. Annals of Indian Academy of Neurology. 2017 Apr 1;20(2):116.
23. Gaspard N, Foreman BP, Alvarez V, Kang CC, Probasco JC, Jongeling AC, Meyers E, Espinera A, Haas KF, Schmitt SE, Gerard EE. New-onset refractory status epilepticus: etiology, clinical features, and outcome. Neurology. 2015 Nov 3;85(18):1604-13
24. Dubey D, Kalita J, Misra UK. Status epilepticus: Refractory and super-refractory. Neurology India. 2017 Mar 1;65(7):12.
25. Samanta D, Garrity L, Arya R. Refractory and Super-refractory Status Epilepticus. Indian Pediatr. 2020 Mar 15;57(3):239-253. doi: 10.1007/s13312-020-1759-0.
26. Cascino GD, Hesdorffer D, Logroscino G, Hauser WA. Morbidity of nonfebrile status epilepticus in Rochester, Minnesota, 1965–1984. Epilepsia. 1998 Aug;39(8):829-32
27. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, Garnett L, Fortner CA, Ko D. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology. 1996 Apr 1;46(4):1029-35.
28. Delaj L, Novy J, Ryvlin P, Marchi NA, Rossetti AO. Refractory and super-refractory status epilepticus in adults: a 9-year cohort study. Acta Neurologica Scandinavica. 2017 Jan;135(1):92-9
29. Hassan H, Rajiv KR, Menon R, Menon D, Nair M, Radhakrishnan A. An audit of the predictors of outcome in status epilepticus from a resource-poor country: a comparison with developed countries. Epileptic Disorders. 2016 Jun;18(2):163-72
30. Murthy JM. Refractory status epilepticus. Neurology India. 2006 Oct 1;54(4):354.

31. Wilder-Smith EP, Lim EC, Teoh HL, Sharma VK, Tan JJ, Chan BP, Ong BK. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. Annals-Academy Of Medicine Singapore. 2005 Aug 1;34(7):417
32. Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia. 2010 Feb;51(2):251.
33. Gaspard N, Hirsch LJ, Sculier C, Loddenkemper T, van Baalen A, Lancrenon J, Emmery M, Specchio N, Farias-Moeller R, Wong N, Nabbout R. New-onset refractory status epilepticus (NORSE) and febrile infection–related epilepsy syndrome (FIRES): state of the art and perspectives. Epilepsia. 2018 Apr;59(4):745-52.
34. Khawaja AM, DeWolfe JL, Miller DW, Szaflarski JP. New-onset refractory status epilepticus (NORSE)—the potential role for immunotherapy. Epilepsy & Behavior. 2015 Jun 1;47:17-23
35. Van Lierde I, Van Paesschen W, Dupont P, Maes A, Sciot R. De novo cryptogenic refractory multifocal febrile status epilepticus in the young adult: a review of six cases. Acta neurologica belgica. 2003 Jun 1;103(2):88-94.
36. Costello DJ, Kilbride RD, Cole AJ. Cryptogenic new onset refractory status epilepticus (NORSE) in adults—infectious or not?. Journal of the neurological sciences. 2009 Feb 15;277(1-2):26-31.
37. Miyahara A, Saito Y, Sugai K, Nakagawa E, Sakuma H, Komaki H, Sasaki M. Reassessment of phenytoin for treatment of late stage progressive myoclonus epilepsy complicated with status epilepticus. Epilepsy research. 2009 Apr 1;84(2-3):201-9.
38. Tassinari CA, Dravet C, Roger J, Cano JP, Gastaut H. Tonic status epilepticus precipitated by intravenous benzodiazepine in five patients with Lennox-Gastaut syndrome. Epilepsia. 1972 Jul;13(3):421-35.
39. Nobutoki T, Sugai K, Fukumizu M, Hanaoka S, Sasaki M. Continuous midazolam infusion for refractory nonconvulsive status epilepticus in children. No to Hattatsu= Brain and Development. 2005 Sep 1;37(5):369-73

40. Sutter R, Marsch S, Fuhr P, Rüegg S. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7‐year observational study. Epilepsia. 2013 Mar;54(3):502-11
41. Kim MA, Park KM, Kim SE, Oh MK. Acute symptomatic seizures in CNS infection. European Journal of Neurology. 2008 Jan;15(1):38-41.
42. Casado-Flores J, Rodrigo C, Arístegui J, Martínón JM, Fenoll A, Mendez C. Decline in pneumococcal meningitis in Spain after introduction of the heptavalent pneumococcal conjugate vaccine. The Pediatric infectious disease journal. 2008 Nov 1;27(11):1020-2
43. Zoons E, Weisfelt M, de Gans J, Spanjaard L, Koelman JH, Reitsma JB, van de Beek D. Seizures in adults with bacterial meningitis. Neurology.2008;70(22 Pt 2):2109–15.
44. Phillips SA, Shanahan RJ. Etiology and mortality of status epilepticus in children: a recent update. Archives of Neurology. 1989 Jan 1;46(1):74-6.
45. Chang CJ, Chang HW, Chang WN, Huang LT, Huang SC, Chang YC, Hung PL, Chang CS, Chuang YC, Huang CR, Tsai NW. Seizures complicating infantile and childhood bacterial meningitis. Pediatric neurology. 2004 Sep 1;31(3):165-71
46. Lowenstein DH, Alldredge BK. Status epilepticus. New England Journal of Medicine. 1998 Apr 2;338(14):970-6.
47. Outin H, Blanc T, Vinatier I. Emergency and intensive care unit management of status epilepticus in adult patients and children (new-born excluded). Société de réanimation de langue française experts recommendations. Revue neurologique. 2009 Apr;165(4):297-305.
48. Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, Holtkamp M. EFNS guideline on the management of status epilepticus in adults. European journal of neurology. 2010 Mar;17(3):348-55.
49 Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE. A comparison of four treatments for generalized convulsive status epilepticus. New England Journal of Medicine. 1998 Sep 17;339(12):792-8.

50 Aminoff MJ. Do nonconvulsive seizures damage the brain?—No. Archives of neurology. 1998 Jan 1;55(1):119-20.

51 Drislane FW. Evidence against permanent neurologic damage from nonconvulsive status epilepticus. Journal of Clinical Neurophysiology. 1999 Jul 1;16(4):323-31

52 Jordan KG, Hirsch LJ. In nonconvulsive status epilepticus (NCSE), treat to burst-suppression: pro and con. Epilepsia. 2006 Oct;47:41-5.

53 Kaplan PW. No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or:«the cure may be worse than the disease»). Neurophysiologie Clinique/Clinical Neurophysiology. 2000 Dec 1;30(6):377-82

54 Young GB, Jordan KG. Do nonconvulsive seizures damage the brain?—Yes. Archives of neurology. 1998 Jan 1;55(1):117-9.

55 Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. Archives of neurology. 2005 Nov 1;62(11):1698-702

56 Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain. 2012 Aug 1;135(8):2314-28

57 Shimizu M, Kagawa A, Takano T, Masai H, Miwa Y. Neurogenic stunned myocardium associated with status epileptics and postictal catecholamine surge. Internal Medicine. 2008;47(4):269-73

58 Manno EM, Pfeifer EA, Cascino GD, Noe KH, Wijdicks EF. Cardiac pathology in status epilepticus. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2005 Dec;58(6):954-7.

59 Kurukumbi M, Solieman N, Al-Hamad S, Bhandary S, Yusuf N, Jayam-Trouth A. Prognostication of electrocardiographic changes with status epilepticus in African American population. Journal of Neurology Research. 2014 Jul 3;4(2-3):63-71.

60 Boggs JG, Painter JA, DeLorenzo RJ. Analysis of electrocardiographic changes in status epilepticus. Epilepsy research. 1993 Jan 1;14(1):87-94.

61 Stein PK, Domitrovich PP, Huikuri HV, Kleiger RE, Cast Investigators. Traditional and nonlinear heart rate variability are each independently associated with mortality after myocardial infarction. Journal of cardiovascular electrophysiology. 2005 Jan;16(1):13-20.

62 Mukherjee S, Tripathi M, Chandra PS, Yadav R, Choudhary N, Sagar R, Bhore R, Pandey RM, Deepak KK. Cardiovascular autonomic functions in well-controlled and intractable partial epilepsies. Epilepsy research. 2009 Aug 1;85(2-3):261-9.

63 Lanigar S, Selwa L. An Analysis Of Heart Rate Variability In Patients In Status Epilepticus. In Epilepsia 2008 Jan 1 (Vol. 49, pp. 18-18).

64 Meierkord H, Holtkamp M. Non-convulsive status epilepticus in adults: clinical forms and treatment. The Lancet Neurology. 2007 Apr 1;6(4):329-39.

65 Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004 May 25;62(10):1743-8.

66 Derbyshire AJ, Rempel B, Forbes A, Lambert EF. The effects of anesthetics on action potentials in the cerebral cortex of the cat. Am J Physiol 1936;116:577–96

67 Electrophysiology TF. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation. 1996 Mar 1;93(5):1043-65

68 Sammito S, Böckelmann I. Reference values for time-and frequency-domain heart rate variability measures. Heart Rhythm. 2016 Jun 1;13(6):1309-16.

69 Dubey D, Bhoi SK, Kalita J, Misra UK. Spectrum and predictors of refractory status epilepticus in a developing country. Canadian Journal of Neurological Sciences. 2017 Sep;44(5):538-46

70 Jayalakshmi S, Ruikar D, Alladi S, Sahu S, Kaul S, Mohandas S. Determinants and predictors of outcome in super refractory status epilepticus—a developing country perspective. Epilepsy research. 2014 Nov 1;108(9):1609-17

71 Sinha S, Prashantha DK, Thennarasu K, Rao GU, Satishchandra P. Refractory status epilepticus: a developing country perspective. Journal of the neurological sciences. 2010 Mar 15;290(1-2):60-5.

72 Giovannini G, Monti G, Polisi MM, Mirandola L, Marudi A, Pinelli G, Valzania F, Girardis M, Nichelli PF, Meletti S. A one-year prospective study of refractory status epilepticus in Modena, Italy. Epilepsy & Behavior. 2015 Aug 1;49:141-5

73 Hocker SE, Britton JW, Mandrekar JN, Wijdicks EF, Rabinstein AA. Predictors of outcome in refractory status epilepticus. JAMA Neurol. 2013;70(1):72-7; Available at: http://jamanetwork.com/journals/jamaneurology/fullarticle/1557592. Accessed January 24, 2017

74 Vooturi S, Jayalakshmi S, Sahu S, Mohandas S. Prognosis and predictors of outcome of refractory generalized convulsive status epilepticus in adults treated in neurointensive care unit. Clinical neurology and neurosurgery. 2014 Nov 1;126:7-10.

75 Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. Epilepsia. 2002 Aug;43(8):847-54.

76 Nei M, Ho RT, Sperling MR. EKG abnormalities during partial seizures in refractory epilepsy. Epilepsia. 2000 May;41(5):542-8.

77 Derbyshire AJ, Rempel B, Forbes A, Lambert EF. The effects of anesthetics on action potentials in the cerebral cortex of the cat. Am J Physiol 1936;116:577–96

78 Faria MT, Rego R, Rocha H, Sá F, Farinha R, Oliveira A, Barata P, Alves D, Pereira J, Rocha-Gonçalves F, Gonçalves H. cTnI, BNP and CRP profiling after seizures in patients with drug-resistant epilepsy. Seizure. 2020 Aug 1;80:100-8.

79 Treiman DM. Electroclinical features of status epilepticus. J Clin Neurophysiol .1995;12:343–62.

80 Ibrahim A, Megahed A, Salem A, Zekry O. Impact of Cardiac Injury on the Clinical Outcome of Children with Convulsive Status Epilepticus. Children (Basel). 2022 Jan 18;9(2):122.

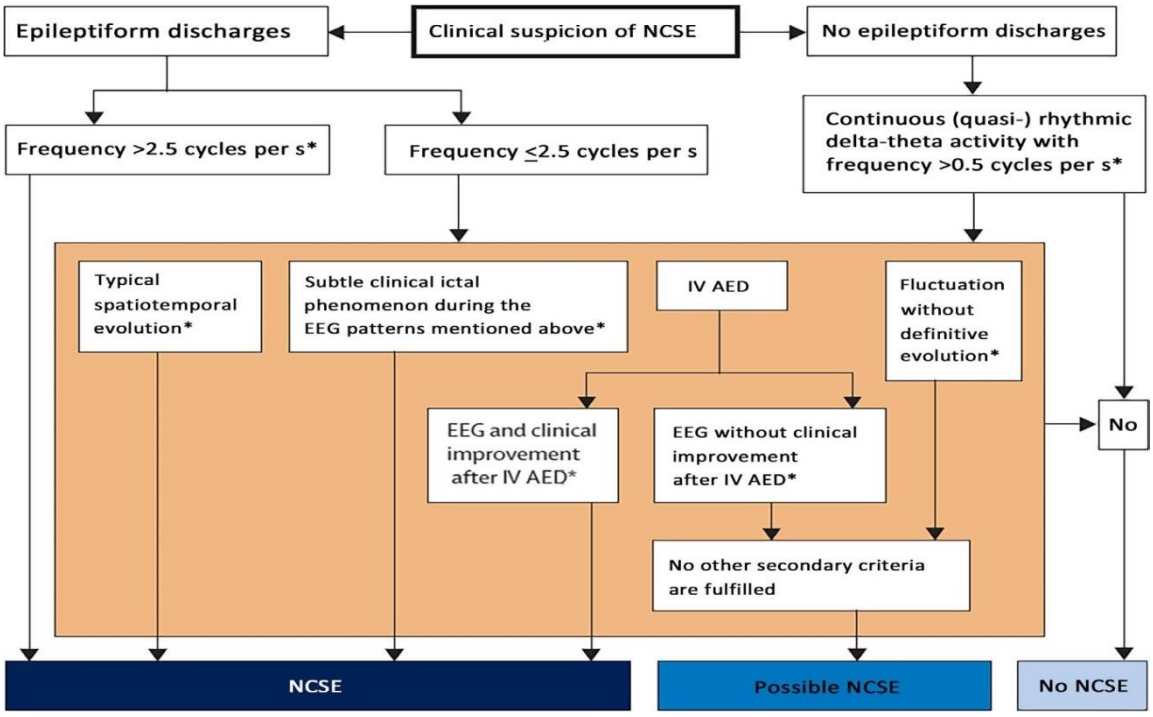
ANNEXURE - 1

Definition of Status Epilepticus as per ILAE 2015

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected		
Type of SE	Operational dimension 1Time (t1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired	10 min	>60 min
consciousness		
Absence status epilepticus	10–15 mina	Unknown
aEvidence for the time frame is currently limited and future data may lead to modifications.		

ANNEXURE - 2

Salzburg EEG criteria for the diagnosis of NCSE



ANNEXURE - 3

Specifications for the Salzburg criteria

Frequency of the epileptiform discharges

Frequency higher than 2·5 cycles per s is considered when more than 25 epileptiform discharges are seen per 10 s epoch.

Continuous (quasi-)rhythmic delta-theta activity Repetition of waveforms with relatively uniform morphology and duration, and without an interval between consecutive waveforms. The duration of one cycle (ie, the period) of the rhythmic pattern should vary by less than 50% from the duration of the subsequent cycle for most (>50%) cycle pairs to qualify as rhythmic.

Typical spatiotemporal evolution

Sequential change in voltage and frequency, or evolution in frequency and change in location:

- Change in voltage (increase or decrease) with a minimum factor of two of the voltages measured between the first and last graphoelement.
- Change in frequency more than 1 Hz: frequency of the second with highest rate of graphoelements and the second with lowest rate of graphoelements di□ered by more than 1 Hz.
- Evolution in frequency is defined as at least two consecutive changes in the same direction by at least 0·5 per s.
- Change in location sequential spreading into or out of at least two di□erent standard 10–20 electrode locations.
- To qualify as present, a single frequency or location must persist at least three cycles. The criteria for evolution must be reached without the pattern remaining unchanged in frequency, morphology, or location for 5 min or more.

Fluctuation without definite evolution

Three or more changes, not more than 1 min apart, in frequency (by at least 0·5 per s) or three or more changes in location (by at least one standard interelectrode distance), but not qualifying as evolving.

ANNEXURE - 4
Management of SE and RSE

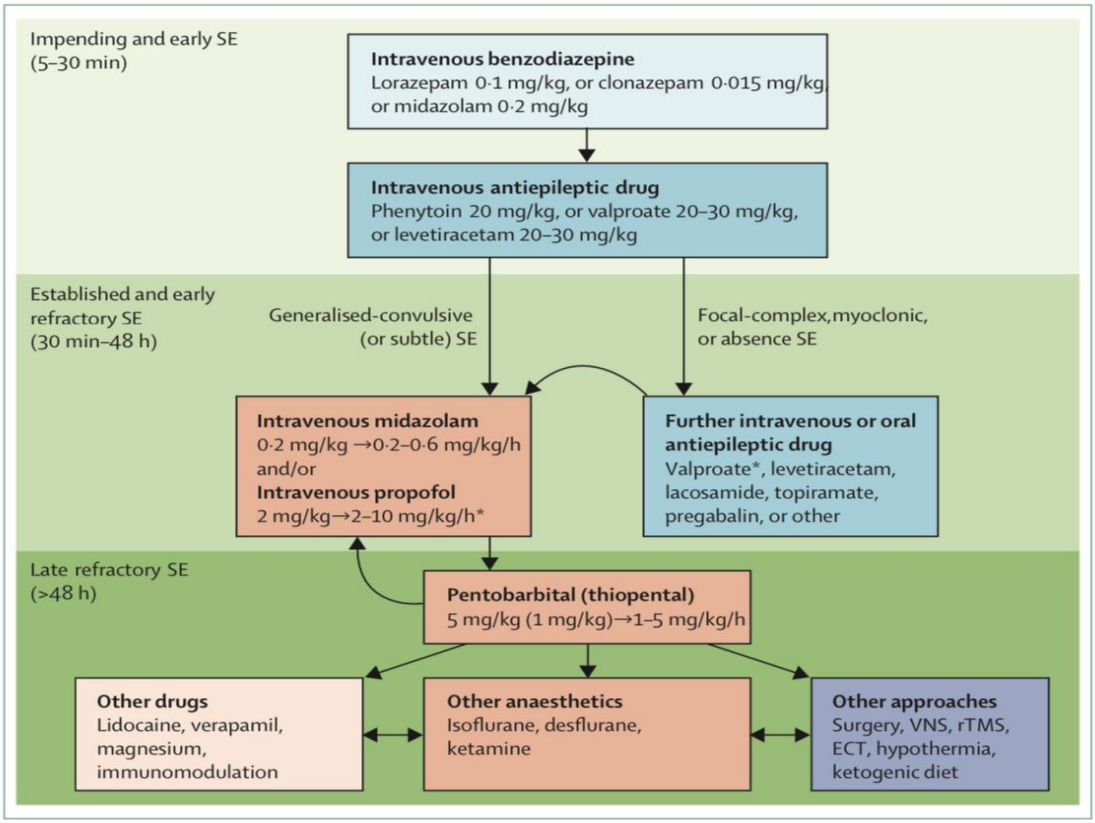


Figure: **Status epilepticus treatment**
Increasing refractoriness is indicated by the background green intensity. Light blue=first-line drugs. Dark blue=second-line drugs. Orange=third line drugs. *Great caution is needed for use of valproate in children younger than 2 years (because of hepatic toxicity), and propofol in young children (because of propofol infusion syndrome). In this setting, benzodiazepines, phenytoin, and barbiturates are the most widely used options. VNS=vagus nerve stimulation. rTMS=repetitive transcranial magnetic stimulation. ECT=electroconvulsive therapy. SE=status epilepticus.

ANNEXURE - 5
Institution Ethics Committee Certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3566 Date: 12/03/2021

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3401**

Project title: **"Cardiac abnormalities in refractory status epilepticus"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**D.M. Dissertation**
Student Name:	**Dr. Deepika Saroha**
Guide:	**Dr. Samhita Panda**
Co-Guide:	**Dr. Surender Deora & Dr. Sadik Mohammed**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS, Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

ANNEXURE - 6

Patient Proforma

BASIC PATIENT DETAILS	
DATE	
NAME	
AGE	
GENDER	
PHONE NO.	
ADDRESS	
PATIENT ID	
DATE OF ADMISSION DATE OF DISCHARGE /DEATH DATE OF FOLLOW UP (AT 30 DAYS)	

SOCIO-DEMOGRAPHIC DETAILS	
EDUCATION (ILLITERATE/PRIMARY /MIDDLE /HIGH SCHOOL/ GRADUATE AND ABOVE)	
OCCUPATION (UNEMPLOYED/FARMER/SEMISKILLED/SKILLED WORKER/PROFESSIONAL/STUDENT/HOUSE WIFE)	
SOCIO ECONOMIC STATUS (UPPER CLASS/UPPER MIDDLE/LOWER MIDDLE /UPPER LOWER/LOWER)	

PREGNANT (YES/NO)	

DISEASE SPECIFIC DETAILS

TIME OF ONSET OF RSE TIME FROM ONSET TO ADMISSION TYPE OF SE **(A) WITH PROMINENT MOTOR SYMPTOMS** A.1 CONVULSIVE SE (CSE, SYNONYM: TONIC–CLONIC SE) A.1.a. GENERALIZED CONVULSIVE A.1.b. FOCAL ONSET EVOLVING INTO BILATERAL CONVULSIVE SE A.1.c. UNKNOWN WHETHER FOCAL OR GENERALIZED A.2 MYOCLONIC SE (PROMINENT EPILEPTIC MYOCLONIC JERKS) A.2.a. WITH COMA A.2.b. WITHOUT COMA A.3 FOCAL MOTOR A.3.a. REPEATED FOCAL MOTOR SEIZURES (JACKSONIAN) A.3.b. EPILEPSIA PARTIALIS CONTINUA (EPC) A.3.c. ADVERSIVE STATUS A.3.d. OCULOCLONIC STATUS A.3.e. ICTAL PARESIS (I.E., FOCAL INHIBITORY SE) A.4 TONIC STATUS A.5 HYPERKINETIC SE (**B) WITHOUT PROMINENT MOTOR SYMPTOMS (I.E., NONCONVULSIVE SE, NCSE)** B.1 NCSE WITH COMA (INCLUDING SO-CALLED "SUBTLE" SE) B.2 NCSE WITHOUT COMA B.2.a. GENERALIZED B.2.a.a TYPICAL ABSENCE STATUS B.2.a.b ATYPICAL ABSENCE STATUS B.2.a.c MYOCLONIC ABSENCE STATUS B.2.b. FOCAL B.2.b.a WITHOUT IMPAIRMENT OF CONSCIOUSNESS (AURA CONTINUA, WITH AUTONOMIC, SENSORY, VISUAL, OLFACTORY, GUSTATORY, EMOTIONAL/ PSYCHIC/EXPERIENTIAL, OR AUDITORY	

SYMPTOMS) B.2.b.b APHASIC STATUS B.2.b.c WITH IMPAIRED CONSCIOUSNESS B.2.C UNKNOWN WHETHER FOCAL OR GENERALIZED B.2.C.A AUTONOMIC SE	
ETIOLOGICAL CAUSE OF SE WITHDRAWAL OF OR LOW LEVELS OF ANTIEPILEPTIC DRUGS METABOLIC DISORDERS CEREBROVASCULAR DISEASES CNS INFECTIONS NEURODEGENERATIVE DISEASES INTRACRANIAL TUMORS HEAD TRAUMA ALCOHOL RELATED TOXIN CEREBRAL HYPOXIA OR ANOXIA AUTOIMMUNE DISORDERS CAUSING SE MITOCHONDRIAL DISEASES CAUSING SE CHROMOSOMAL ABERRATIONS AND GENETIC ANOMALIES NEUROCUTANEOUS SYNDROMES OTHERS-PREGNANCY -FEVER	
PAST HISTORY OF SE (YES/NO)	
TREATMENT HISTORY ON AEDS (YES/NO)	
CARDIAC RISK FACTORS – HYPERTENSION DIABETES HYPERLIPIDEMIA SMOKER	

NEUROLOGICAL EXAMINATION	
HIGHER MENTAL FUNCTION	
CRANIAL NERVES	

MOTOR SYSTEM	
SENSORY SYSTEM	
CEREBELLUM	
DIAGNOSIS	

	BASELINE AT ADMISSION	END OF HOSPITAL STAY	30 DAYS
GCS			
MRS			
TROP I			NIL
NT-Pro BNP			NIL
CARDIAC EVENTS RECORDED			
ARRYTHMIA TYPE DURATION			
CONDUCTION ABNORMALITIES			
HR VARIABILITY			
ECG			
2D ECHO			

NEUROIMAGING PROFILE	
MRI BRAIN CT HEAD	

ELECTROPHYSIOLOGICAL CHANGES	
State of consciousness	
Background rhythm	
Pattern of discharges (if any)	
Electrographic seizure(yes/no)	
Definite NCSE/Possible NCSE/ No NCSE	

Burst Suppression Pattern (yes/no) If yes,duration of burst suppression	
Seizure recorded in 24 hour If yes-type Localization a/w arrhythmia time b/w seizure onset and arrythmia	

ANNEXURE - 7

Informed Consent Form (English)

All India Institute of Medical Sciences, Jodhpur, Rajasthan
Department Of Neurology

TITLE OF THESIS: CARDIAC ABNORMALITIES IN REFRACTORY STATUS EPILEPTICUS

NAME OF INVESTIGATING STUDENT: DR. DEEPIKA SAROHA
MOBILE NO.8860138329

I …… s/d/w of ……, a resident of ……,hereby declare that I give my full free and voluntary informed consent to participate in the Thesis study labelled "**CARDIAC ABNORMALITIES IN REFRACTORY STATUS EPILEPTICUS** ".

Dr. Deepika Saroha has informed me to my full satisfaction in the language I understand, about the purpose, and nature of study and various investigations to be carried out for the study. I have been informed about the duration of the study and possible complications caused by study. I give full consent for being enrolled in the above study and I reserve my rights to withdraw from the study whenever I wish without prejudice of my right to undergo further treatment at this hospital and its associated hospitals.

Date: _____ _____
Place: _____ Signature/Left thumb impression

This is to certify that the above consent has been obtained in my presence.

Date: _____ _____
Place: _____ Signature of PG student

Witness1 Wiitness 2
Signature Signature

Informed Consent Form (Hindi)

अखिल भारतीय आयुर्विज्ञान संस्थान , जोधपुर, राजस्थान

सहमति पत्र

मैं ----------पुत्र / पुत्री / पत्नी----------निवासी ----------
----
यह घोषणाकरता /करती हूँ की मुझे इस अध्ययन के उद्देष्यों व इस मेहोने वाली गितिविधयो के बारे मे सूचित किया गया हैजिससे मैं पूर्णतः संतुष्ट हूँ और मुझे प्रश्न पूछने का अवसरदिया गया है I ई. ई. जी., ई. सी. जी.
,हॉलटर, २ डी इकोऔर २ मी. ली. अतिरिक्त खून की जाँच की जाएगी जिससेट्रोपीनिन आई , एन. टी. प्रो., बी. एन. पी. व मेरी बीमारी वजांचो का अवलोकन किया जायेगा I मुझे ज्ञात है की मै इसअधयन से अपनी सहमती वापिस लेने के लिए सवतंत्र हूँऔर मैं किसी भी वक्त अप नी मर्ज़ी से इस अधयन को छोडसकता /ती हूँ और इसका प्रतिकूल प्रभाव मेरे और मेरेपरिवा र के ऐम्स , जोधपुर अस्पताल मे चल रहे इलाज परनही पडेगा I
मुझे यह भी ज्ञात है की इलाज चिकित्सक किसी भी समयअधयन मे मेरी भागीदारी को रोक सकता है लेकिन किसी भीहालत मे मेरे स्वास्थ्य या इलाज को (अध्ययन के दौरान याबाद मे) खतरे मे नही डाला जायेगा I मुझे जानकारी है कीमुझसे ली गयी जानकारी को एक डाटाबे स मे दर्ज कियाजायेगा और इसे प्रकाशित भी किया जा सकता है लेकिनमुझ से ली गयी कोई भी जानकारी की गोपनीयता कोबनाये रखा जायेगा और मेरी पहचान का विवरण कही भी उजागर नही किया जायेगा ,जब तक की कानून याविनयामक एजेंसियों दारा इसकी मांग न की जाये I
रोगी / क़ानूनी रूप से स्वीकृत प्रतिनिधि के हस्ताक्षर याअंगूठे का निशान

नाम
दिनांक स्थान

अन्वेषक का नाम व हस्ताक्षर,

दिनांक स्थान

मैं यह प्रमाणित करता /करती हूँ की अन्वेषक ने इस सुचनापत्र और रोगी जानकारी प्रपत्र की सामग्री को पढ़करप्रतिभागी को उसके समझ आने वाली भाषा में सुना दिया हैव प्रतिभागी ने उसे समझ लिया है।

साक्षी का नाम व हस्ताक्षर,
दिनांक स्थान

ANNEXURE - 8

Patient Information Sheet (English)

All India Institute of Medical Sciences, Jodhpur, Rajasthan

Department Of Neurology

You are being invited to participate in research study.

Before you take part in this research study, we wish to explain the study to you and give you the chance to ask questions. Please read carefully the information provided here. If you agree to participate please sign the informed consent form.

TITLE: - CARDIAC ABNORMALITIES IN REFRACTORY STATUS EPILEPTICUS

Investigator: Dr. Deepika Saroha

PURPOSE OF THE RESERCH STUDY: The aim and objective of the study is to assess cardiac abnormalities including electrocardiographic changes in patient of refractory status epilepticus and to correlate these cardiac abnormalities with patients outcome

STUDY PROCEDURES AND VISIT SCHEDULE: we are doing a prospective observational study in which we will do EEG, ECG, 2 D ECHO , holter and relevant hematological investigation including troponin I and NT pro BNP and assessing cardiac complications in refractory status epilepticus.

WITHDRAWAL FROM STUDY: You have the right to withdraw yourself from the study at any time during the course of the study without any prejudice to you or your family's right to undergo future treatment at AIIMS Jodhpur

Patient Information Sheet (Hindi)

अखिल भारतीय आयुर्विज्ञान संस्थान , जोधपुर, राजस्थान

रोगी सुचना प्रपत्र

शीर्षक : दुर्दम्य स्थिति मिर्गी में ह्रदय सम्बन्धी
अन्वेषक : - डॉ. दीपिका सरोहा
स्थान- ऐम्स , जोधपुर
आपको ये प्रपत्र इसलिए दिया गया है क्योंकि आप दुर्दम्य स्थिति मिर्गी से पीड़ित है। उपरलिखित अध्ययन में भाग लेने का निर्णय करने से पहले कृपया इस प्रपत्र को ध्यानपूर्वक पढ़ लें।
अगर आप जानकारी चाहते है तो जांचकर्ता से संपर्क कर सकते है। आपसे अपेक्षा की जाती है की अगर आप इस अध्ययन में भाग लेने का निर्णय करते है तो जांचकर्ता से संपर्क कर सकते है। संलगन सूचित सहमति पत्र पर हस्ताक्षर करे व इस अध्ययन की गतिविधियों में भाग लें। क्योंकि आप दुर्दम्य स्थिति मिर्गी से पीड़ित है इसलिए आपकी आपके चिकित्सक द्वारा सामान्यतः रक्त की जाँच करवाई जाएगी। ई. ई. जी., इको और ऍम.आर.आई. कराई जाएगी।
इस अध्ययन के तहत मैं सिर्फ इन जांचो की रिपोर्टों का अवलोकन करुँगी और इनको एक परफोर्मा और कम्प्यूटरकृत डेटाबेस में प्रविष्ट करुँगी। इस अध्ययन के तहत एक टेरोपिनान आई और ऐन. टी. प्रो. विनयी जाँच का नमूना लिया जायेगा। जिसके लिए करीब २ मी.ली. रक्त लिया जायेगा। इसके लिए आपका कोई खर्च नहीं आएगा। आपकी जांचो को ह्रदय सम्बन्धी जटिलताओं से जोड़ कर देखा जायेगा जोकि आगे जाकर और मरीजों के लिए कामयाब हो सकता है। इस अध्ययन में भाग लेने से आप को कोई सीधा लाभ नहीं मिल रहा है।

ANNEXURE – 9

Declaration by the PG Student

All India Institute of Medical Sciences Jodhpur, Rajasthan

I hereby declare that:

1. The study will be done as per ICMR/ GCP guidelines.
2. The study has not been initiated and shall be initiated only after ethical clearance
3. Voluntary written consent of the volunteers/patients will be obtained.
4. In case of children and mentally handicapped volunteers/patients, voluntary written informed consent of the parents/guardians will be obtained.
5. The probable risks involved in the study will be explained in full to the subjects/parents/guardians in their own language.
6. Volunteers/patients/parents/guardians will be at liberty to opt out of the study at any time without assigning reason.
7. I will terminate the study at any stage, if I have probable cause to believe, in the exercise of the good faith, skill and careful judgement required for me that continuation of the study/experiment is likely to result in injury/disability/death to the volunteers/subject.

Date: _____

(Signature of Guide/Supervisor/s) **Department _**