SERUM LEVELS OF CARDIAC TROPONIN-T IN ADULT PATIENTS WITH EPILEPSY

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Declaration

I, Dimakatso Sethepele Ansion Makwela, do hereby declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the division of Neurology. This research report is submitted in the publishable format as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other university.

The …21st……. day of September… 2020

For Lesedi Maphume

ABSTRACT

BACKROUND: Myocardial infarctions have been reported in association with seizures. In older age groups, an elevated risk of myocardial injury exists through the presence of vascular risk factors such as hypertension, diabetes and dyslipidemia. Elevated cardiac specific troponins in an epileptic patient suggest the probability of cardiac ischemia.

AIMS: Firstly, to compare cardiac troponin-T (cTnT) levels in patients with different causes and severity of epilepsy, within seven days of having had a seizure. Secondly, to assess if elevated cTnT levels in patients with epilepsy are associated with the presence of cardiovascular risk factors.

METHODS: This prospective study included 122 adult epilepsy patients, recruited over a period of approximately 7 months, who presented within 7 days of having had a seizure at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH). The patients were noted to have presented with either status epilepticus, stable or unstable epilepsy.

RESULTS: The mean age was 43.6 years with a range of 18 to 85 years. Cardiac troponin-T levels were elevated in 24(19.6%) patients, 15 of whom had presented in status epilepticus. Twenty-six subjects were over 60 years in age. In this older age group, 17 (65.3%) had elevated cTnT levels. Of a total of 26 hypertensive patients, 13 (50.0%) had elevated cTnT, moreover, of 11 diabetic patients, 7 (63.6%) were also found to have elevated cTnT levels.

CONCLUSION: Troponin-T levels were found to be elevated in patients with epilepsy. This sensitive marker of cardiac tissue injury being elevated adds some support to the notion that myocardial injury can occur as a complication of seizures. Patients with complicated epilepsy,

such as status epilepticus, the elderly and patients with vascular risk factors, are at particular risk for myocardial injury when they have seizures.

Keywords: epilepsy, seizures, cardiac troponins

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Abbreviations

ACS	acute coronary syndrome
ANS	autonomic nervous system
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CT	computed tomography
cTnI	cardiac troponin-I
cTnT	cardiac troponin-T
cTnT- hs	cardiac troponin-T high sensitivity
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
GTC	generalized tonic-clonic
HJH	Helen Joseph Hospital
h	hours
ILAE	International League Against Epilepsy
min	minutes
MRI	magnetic resonance imaging
ng/L	nanograms per liter
NHLS	National Health Laboratory Service
SD	standard deviation
SUDEP	sudden unexpected death in epilepsy
WHO	World Health Organization

CHAPTER 1: PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 INTRODUCTION

The International League Against Epilepsy (ILAE) defines epilepsy as 'a disorder of the brain that is characterized by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition' (Fisher et al., 2014) and an epileptic seizure as 'a transient occurrence of signs and/ or symptoms due to excessive or synchronous neuronal activity in the brain' (Fisher et al., 2005; Maloney et al., 2019). In 2013, the ILAE Executive Committee adopted recommendations by the Task Force of the ILAE for a diagnosis of epilepsy to be made if any of the following conditions are met;

- At least two unprovoked or reflex seizures occurring more than 24 hours apart.
- One unprovoked or reflex seizure and a probability of further seizures similar to the general recurrence risk of at least 60% after two unprovoked seizures occurring over the next 10 years.
- A diagnosis of an epilepsy syndrome (Fisher et al., 2014; Sirven et al., 2015)

The previous definition of epilepsy required two unprovoked seizures occurring at least 24 hours apart. In contrast, the latest definition allows for the need to address circumstances of high risk for future seizures after the first unprovoked seizure (Fisher et al., 2014).

1.2 EPIDEMIOLOGY

Epilepsy is a common neurological disorder that affects over 70 million people worldwide (Ackermann et al., 2019) and contributes 1% of global disease burden (Samia et al., 2019). The

median prevalence of active epilepsy in high income countries was reported to be 4.9 per 1000 compared to 12.7 per 1000 in rural areas of resource limited countries (Samia et al., 2019). Estimates of incidence from African studies range from 64 to 215/ 100 000 people per year. In southern and eastern sub-Saharan Africa, epilepsy ranks 19th in its contribution to the total disease burden (Wagner et al., 2015). Standardized mortality ratio by a Kenyan study which measures mortality adjusted for the age structure of the population in people with convulsive epilepsy was at 6.5 (95% CI: 5.0- 8.3)(Samia et al., 2019).

In South Africa, Christianson et al., 2000, reported the lifetime and active prevalence of epilepsy in rural children at 7.3/1,000 and 6.7/1,000 respectively. A second study by Wagner et al., 2015, reported a crude incidence of 17.4/ 100 000 per year (95% CI: 13.1-23.0) for convulsive epilepsy in South Africa. The standardized mortality rate in this study was reported at 2.6 (95% CI: 0.6-36.4). This high disease burden results in several socio-economic impacts, high health utilization, reduced participation in production and work, comorbidities, stigma, behavioral problems, psychological morbidity, poor quality of life and increased mortality rates (Samia et al., 2019).

1.3 CLASSIFICATION OF SEIZURES

Seizure classification begins with eliciting history or an observation of certain symptoms and signs that are known to be associated with common seizure types. The ILAE released the 2017 version of seizure-type classification which is a revision of the classification of the modified 1981 version. This classification addresses several important issues that were not catered for in the 1981 version such as inclusion of some seizure types, consideration that tonic seizure types

can be focal or generalized in onset, and that a seizure is unclassifiable when there's a lack of knowledge about the seizure onset. Depending on the desired degree of information needed, a basic or the expanded version of the 2017 classification of seizures can be applied.

The basic classification allows for seizures to be categorized by onset, as well as into motor or non-motor subcategories, even when the onset of the seizure is unknown. Focal seizures are further classified according to the level of awareness and the classification focal to bilateral tonic-clonic replaces the previous 'focal with secondary generalization'. Unclassified refers to seizure with features that do not fit into any of the categories or where there is a lack of sufficient information on the seizure presentation to allow for categorization (Fisher et al., 2017) Figure 1.1.

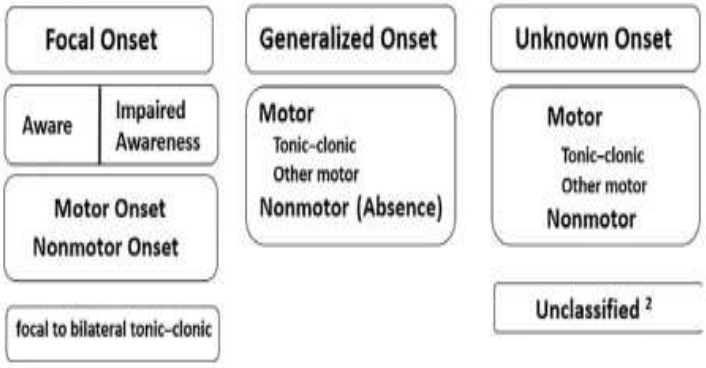

Figure 1.1 ILAE classification of seizure types, basic version

The expanded ILAE operational classification of seizure types allows for classification of seizures based on the earliest prominent feature, be it motor or non-motor in nature, and by giving a description of the said feature.

Patients with epilepsy are considered stable when their disease is controlled and they are not considering withdrawal from medication (Minshall I, 2004).

Status epilepticus is defined by the ILAE Task Force on Classification of Status Epilepticus in 2015 as 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 seizure. It can have long term consequences after 30 minutes including neuronal death, neuronal injury and neuronal network alterations (Trinka et al., 2015).

1.4 CARDIAC COMPLICATIONS OF SEIZURES

1.4.1 The role of the autonomic nervous system (ANS)

The autonomic nervous system (ANS) is responsible for the heart rate, conduction velocity, contractility, excitability and relaxation function, as well as for myocyte homeostasis at a cellular/molecular level. Epilepsy causes autonomic imbalance which results in autonomic dysfunction thereby causing increased sympathetic tone and lower vagal tone. This causes catecholamine toxicity which promotes myocyte apoptosis, inflammation and histological contraction band necrosis (Fialho et al., 2019). Cortical structures that play a role in influencing the ANS include the insular, anterior cingulate,

posterior orbito-frontal and prefrontal cortices along with the amygdala and the hypothalamus. Ictal discharges that occur in or propagate to these regions can commonly result in increased sympathetic outflow resulting in tachycardia, however, parasympathetic responses such as bradycardia can occur if ictal discharges occur in cortical areas that govern depressor responses (Eggleston et al., 2014).

1.4.2 Cardiac ischemia

Myocardial infarctions have been reported as a complication of seizures (Montepietra et al., 2009). Seizures are associated with sympathetic discharge, resulting in increased cardiac output, tachycardia, hypertension and tachypnea. These assist in meeting the increased metabolic rate of the convulsing brain. The enhanced myocardial contractility, tachycardia, hypertension, and augmented cardiac afterload from tonic muscle contractions results in increased myocardial oxygen demand (Alehan et al., 2009; Fawaz et al., 2014; Hajsadeghi et al., 2009). Furthermore, ictal apneic episodes contribute to hypoxia and exaggerated myocardial metabolic demand as well as oxygen supply mismatch, which may result in myocardial ischemia (Eskandarian et al., 2011; Hajsadeghi et al., 2014; Woodruff et al., 2003). Additionally, increased cardiac contractile activity may dislodge preexisting plaque, resulting in acute coronary ischemia (Eskandarian et al., 2011; Montepietra et al., 2009).

In older age groups, elevated risk of myocardial injury exists, through the presence of vascular risk factors such as hypertension, diabetes and dyslipidemia (Fawaz et al., 2014). Elevated troponin-I levels of unknown origin have been found to be associated with

vascular risk factors. This is hypothesized to be due to “reversible ischemia model”. Such ischemia may be secondary to transitory reductions in coronary flow or an autonomic dysregulation, resulting from central nervous system induced sympathetic overactivity (Sieweke et al., 2012).

1.5 CARDIAC TROPONINS

Troponin regulatory proteins, consisting of troponin-T and troponin-I, which are unique to cardiac muscle, and troponin-C, are part of the thin filament contractile proteins and play a role in controlling the contraction and relaxation of skeletal and cardiac muscle. Troponin-I inhibits actin-myosin interaction, while troponin-T binds the troponin complex to tropomyosin and stabilize the complex on the actin filament (Alehan et al., 2009; Khattab et al., 2014; Woodruff et al., 2003). Serum concentrations of cardiac troponins are sensitive markers of myocardial necrosis and they can be found to be elevated in mild damage of cardiac tissue without necrosis or acute ischemia (Alehan et al., 2009; Eskandarian et al., 2011). They have been designated the preferred biomarker for the diagnosis of acute myocardial infarction (El Amrousy et al., 2017; Hocker et al., 2013).

Detection of cardiac troponins is not pathognomic of acute coronary syndrome but rather suggests myocardial injury of any cause and may be found in non-coronary artery related conditions. Elevated cardiac troponins have a strong correlation with adverse outcome whether coronary artery disease is present or not (Al-Otaiby et al., 2011; Marini et al., 2013). Early release kinetics allows for their detection at 3-6 hours after symptom onset during myocardial infarction, with peaks at 12-48 hours and they may remain elevated for 7-14 days

(Al-Otaiby et al., 2011; Eskandarian et al., 2011; Marini et al., 2013). Troponin-T has a shorter half -life of about 90min and persistent elevation on day 3 or 4 reflects degradation of the contractile elements which is a hallmark of irreversible cell injury (Al-Otaiby et al., 2011 Eisenman, 2006). Troponins are thus sensitive markers of cardiac tissue injury. Specificity is limited as elevations can occur in non-ischemic cardiac disease such as cardiomyopathy, tachycardia, heart failure and myopericarditis, as well as in acute neurological disorders like stroke, subarachnoid hemorrhage and subdural hemorrhage. Elevated troponin-T levels may also be found in pulmonary embolism, apical ballooning, after strenuous exercise and in high dose chemotherapy (Al-Otaiby et al., 2011; Eskandarian et al., 2011; Parvulescu-Codrea et al., 2006).

A seizure alone does not increase serum troponin levels. Hence, elevated cardiac troponins in an epileptic patient suggest the probability of cardiac ischemia (Chatzikonstantinou et al., 2015; Eskandarian et al., 2011) and/ or acute neurological insults such as severe head injury, subarachnoid hemorrhage, subdural hemorrhage or stroke (Nejm et al., 2016; Parvulescu-Codrea et al., 2006).

1.6 PROTOCOL

1.6.1 PROBLEM STATEMENT

People with epilepsy suffer from excessive premature mortality and have an increased risk of sudden death, at a rate that is 24 times higher than age-matched controls (Nejm et al., 2016; Woodruff et al., 2003). Sudden unexpected death in epilepsy (SUDEP) is considered the potential cause of premature mortality in people with epilepsy. SUDEP has an annual incidence of 3-9 per 1000 in the general epilepsy population and approximately 1 in 150 in patients with drug resistant epilepsy (Nejm et al., 2016). Distinct mechanisms of SUDEP remain unclear, cardiac arrhythmias due to myocardial ischemia and other causes such as electrolyte disturbances, arrhythmogenic drugs or transmission of the epileptic activity via the autonomic nervous system to the heart, as well as central or obstructive apnea are proposed as possible mechanisms (Fawaz et al., 2014; Hocker et al., 2013; Nejm et al., 2016; Woodruff et al., 2003).

1.6.2 JUSTIFICATION

The possibility exists that there is a subgroup of epilepsy patients with vascular risks who have elevated troponin levels when they have seizures. Troponins are marker of cardiac tissue injury and epilepsy patients with increased levels may therefore be at a higher risk for SUDEP. This will assist in deciding whether further cardiac assessment of these patients is necessary

1.6.3 AIM

The aim of this study is to describe the levels of cardiac troponin-T in adult patients with epilepsy who present in status epilepticus, as well as in stable and unstable epilepsy, within 7 days of having had a seizure.

1.6.4 STUDY OBJECTIVES

To compare the levels of cardiac troponin-T in adult patients with stable and unstable epilepsy within 7 days of having had a seizure, as well as in those who present in status epilepticus who are admitted in the emergency department, the medical/ neurology wards or attend the adult epilepsy outpatient departments at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Helen Joseph Hospital (HJH) and the Chris Hani Baragwanath Academic Hospital (CHBAH).

To compare the causes and types of epilepsy, and the antiepileptic drugs used, in stable and unstable epilepsy patients and in those with status epilepticus.

1.6.5 METHODS

Study design

This is a prospective study that will be conducted over a period of two months of 01 December 2018 to 31 January 2019.

Study population/ setting

The study will be conducted at the emergency unit, neurology and adult epilepsy outpatient units and the medical/neurology wards at CMJAH, CHBAH and HJH.

The first 40 of each of the following subgroup of adult epilepsy patients of ages above 18 years, with stable and unstable epilepsy, as well as status epilepticus patients, who present to the hospital units as above, between 01 December 2018 to 31 January 2019 will be included in the study.

Inclusion criteria

All adult patients of ages above 18 years, who have had seizures within 7 days before presenting to the hospital.

Exclusion criteria

Age below 18 years

Pseudo-seizures

History of previous cardiac intervention

Progressive cerebral disorder

Pregnancy

Severe mental retardation

Sepsis

Patients with a history of vigorous exercise

Sampling strategy

A convenience sampling method will be used.

Sampling size

A minimum of 40 patients of each of the subgroups of epilepsy categories i.e. stable and unstable epilepsy patients, as well as patients in status epilepticus, will be recruited to participate in the study.

Measurements instruments/sheet

Data collection will be done using a data collection sheet (Appendix A)

Data collected will include patient's demographic details, the epilepsy characteristics (type and cause of epilepsy, average number of seizures per week, elapsed time since the last seizure and antiepileptic drug history), smoking and alcohol history.

A neurological examination will be performed on the study participants and recorded as 'normal' or 'abnormal'.

The results of the cardiac troponin-T levels, creatinine and biochemistry results will be recorded as 'normal' or 'abnormal'.

The results of the patient's existing imaging study (CT or MRI) as well their existing EEG results, will be recorded as 'normal' or 'abnormal', if they are available from the patient's records, or as 'not applicable', if they are not available or if they have not been done.

Investigations

For each patient, a 2-mL blood sample collected in an ethylenediaminetetraacetic acid (EDTA) tube, will be used to assess cardiac troponin-T concentration (Elecsys cardiac

troponin-T high-sensitivity (cTnT-hs) test from Roche Diagnostics) at the respective hospital National Health Laboratory Service (NHLS). This assay allows for detection of cardiac troponin-T concentration as low as 3ng/L which is below concentration suggested for the diagnosis of myocardial infarction (Woodruff et al., 2003).

Data Collection

Data will be captured and stored on a Microsoft Office Excel spreadsheet

Data Analysis

The sample demographics will be summarized using descriptive statistics, for categorical variables, frequencies and percentages will be reported.

Mean and standard deviations will be reported if the cardiac troponin-T levels are normally distributed and the median and interquartile ratio if the levels are not normally distributed.

Bivariate analysis will be used to test for associations between the cardiac troponin-T levels and each of the subgroups of the epilepsy patients.

Ethics

The protocol has been submitted for ethics approval to the Human Research Ethics Committee of the University of the Witwatersrand.

Consent to partake in the study, including consent for blood sampling, will be obtained from all study participants or the participant's next of kin in case of status epilepticus, interictal or post ictal confusion.

Patient confidentiality will be maintained by assigning the study participants study numbers. Neither participant's names nor hospital numbers will be recorded. Any association between the study numbers, participant's initials and identity of participants will be kept separate.

Study strengths

Data will be collected by a single researcher using data collection sheets. This will ensure that the data is collected in a reliable, standardized manner.

Study limitations

Selection bias, as only patients at tertiary levels hospitals will be assessed.

No prior knowledge/ investigations available as to pre-existing cardiovascular disease.

Time between occurrence of seizures and investigations will not be standardized.

Funding

The Wits University Division of Neurology will fund the cardiac troponin-T tests at R180.00 per patient.

Timing

The participants will be recruited into the study over a 2 month period of 01 December 2018 to 31January 2019 (see Gantt chart below).

Data analysis and the paper write-up will commence post data collection.

	June 2018	July 2018	August 2018	Sept 2018	Oct 2018	Nov 2018	Dec 2018	Jan 2019
Literature review								
Protocol preparation								
Protocol assessment								
Ethics application								
Data Collection								
Data analysis								
Writing up paper								

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CHAPTER 2 PROPOSED MANUSCRIPT

2.1 BACKGROUND

Epilepsy is a common, chronic neurological disorder which is characterized by recurrent, unprovoked seizures (Kwattab et al., 2014). A seizure is a transient occurrence of signs and/ or symptoms due to excessive or synchronous neuronal activity in the brain (Fisher et al., 2005; Maloney et al., 2019).

Myocardial infarctions have been reported as a complication of seizures (Montepietra et al., 2009). Seizures are associated with sympathetic discharge, resulting in increased cardiac output, tachycardia, hypertension and tachypnea to meet the increased metabolic rate of the convulsing brain. The enhanced myocardial contractility, tachycardia, hypertension, and augmented cardiac afterload from tonic muscle contractions results in increased myocardial oxygen demand (Alehan et al., 2009; Fawaz et al., 2014; Hajsadeghi et al., 2009). Furthermore, ictal apneic episodes associated with generalized seizures contribute to hypoxia and exaggerated myocardial metabolic demand as well as oxygen supply mismatch, which may result in myocardial ischemia (Eskandarian et al., 2011; Hajsadeghi et al., 2009; Woodruff et al., 2003). Additionally, increased cardiac contractile activity may dislodge preexisting plaque, resulting in acute coronary ischaemia (Eskandarian et al., 2011; Montepietra et al., 2009).

Due to their associated increased sympathetic tone, seizures can also lead to catecholamine toxicity which results in histological changes such as myocyte apoptosis, inflammation and

contraction band necrosis. Stress related cardiomyopathy secondary to catecholamine toxicity which manifests as heart failure and/ or arrhythmias, occurs in epilepsy and in other conditions such as intracranial hemorrhage, head injuries, stroke, surgery and drug use (Fialho et al., 2019).

Cardiac troponins are preferred biomarkers for the diagnosis of acute myocardial infarction. They can be detected at 3-6 hours after symptom onset during myocardial infarction, with peaks at 12-48 hours and they may remain elevated for 7-14 days (Al-Otaiby et al., 2011; Eisenman, A. 2006; Eskandarian et al., 2011; Marini et al., 2013). However, detection of cardiac troponins is not pathognomic of acute coronary syndrome but rather suggests myocardial injury of any cause and may be found in non-coronary artery related conditions. Elevations can occur in non-ischemic cardiac disease such as cardiomyopathy, tachycardia, heart failure and myopericarditis, as well as in acute neurological disorders like stroke, subarachnoid hemorrhage and subdural hemorrhage. Elevated troponin-T levels may also be found in pulmonary embolism, apical ballooning, after strenuous exercise and in high dose chemotherapy (Al-Otaiby et al., 2011; Eskandarian et al., 2011; Parvulescu-Codrea et al., 2006).

A seizure does not increase serum troponin levels by itself. Hence, elevated cardiac troponins in an epileptic patient suggest the probability of cardiac ischemia (Chatzikonstantinou et al., 2015; Eskandarian et al., 2011)

2.2 METHODS

2.2.1 STUDY DESIGN AND SETTING

The study was a prospective study conducted at the 3 tertiary referral hospitals in Johannesburg, affiliated to the University of the Witwatersrand.

2.2.2 POPULATION AND SAMPLE

One hundred and twenty-two adult patients, who presented within seven days of having had a seizure or in status epilepticus at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH). The patients were recruited from the emergency, neurology and epilepsy outpatient departments and medical and neurology wards. The recruitment period was between 7 January 2019 and 31 July 2019. Clinical history and examination, laboratory, radiology and electrophysiology findings were used to assign patients to the stable or unstable epilepsy, or the status epilepticus groups. Cardiac troponin-T concentrations were assessed using Elecsys cardiac troponin-T high-sensitivity (cTnT-hs) test from Roche Diagnostics at the respective hospital laboratories i.e National Health Laboratory Service (NHLS). This assay allows for detection of cTnT concentration as low as 3ng/L, which is below concentration suggested for the diagnosis of myocardial infarction. All cTnT levels reading below 3ng/L were recorded as 3ng/L to allow for statistical analysis. Cardiac troponin T (cTnT) level of ≥15ng/L is defined to be elevated by the clinical routine diagnostic laboratory/ NHLS.

Exclusion criteria

Patients were excluded if they had pseudo-seizures, a history of previous cardiac intervention, a progressive cerebral disorder, severe mental retardation, sepsis, a history of vigorous exercise or if pregnant.

2.2.3 ETHICS

The study was approved by the University of Witwatersrand Human Research Ethics Committee, approval number M180979. Consent for participation was obtained from the patients or from their next of kin.

2.2.4 DATA COLLECTION

Information was initially recorded on a standardized collection sheet and then captured onto an electronic spreadsheet (MS Excel). No identifying data was entered into the study collection tools, patients were each given a unique study number.

2.2.5 STATISTICAL ANALYSIS

Stata (version 14.2) was used for all statistical analysis. Patient's ages are reported as means with standard deviations (SD). We used a double tailed t test to compare the age of patients with normal and elevated cTnT concentrations. We tabulated cardiovascular risk factors for all patients, i.e. hypertension, diabetes mellitus, hyperlipidemia and smoking, and compared these, and other categorical variables between patients with normal and elevated cTnT levels, using the exact Fisher's test. All statistically significant results were set at p-value of less than 0.05.

2.3 RESULTS

2.3.1 DEMOGRAPHIC DETAILS

The cohort was made up of 122 patients. There were more male patients (56.6%) compared to female patients (43.4%). The majority of patients were black (91.8%), with 5.7% coloured and 2.5% white patients.

The cohort was divided into 3 groups i.e. patients who were stable, patients with unstable epilepsy and those that had status epilepticus. There were no significant differences amongst the groups in terms of gender distribution, racial composition or age.

There were 45.2% female within the stable group, compared to 47.5% within the unstable epilepsy group and 37.5% within the status epilepticus group. Distribution by gender was not statistically significant (p-value = 0.638).

Black patients were prevalent in all the groups, at 92.9% in the stable epilepsy group, 90.0% in the unstable epilepsy group and 92.5% in the status epilepticus group. These differences were not statistically different (p-value = 0.676).

The mean age of the patients in the stable epilepsy group was 44.21 years with a standard deviation (SD) of ±16.88, compared to 43.08 years (±13.49) for those in the unstable epilepsy group and 43.83 years (±18.08) for those in the status epilepticus group. The differences are not statistically different (p-value = 0.950). The age across the cohort ranged from 18 to 85 years (Table 2.1).

Table 2.1: Demographic details

						P-value
		Stable Epilepsy	Unstable Epilepsy	Status Epilepticus	Total	
	n=	42	40	40	122	
Gender	Female	19 (45.2%)	19 (47.5%)	15 (37.5%)	53 (43.4%)	0.638
	Male	23 (54.8%)	21 (52.5%)	25 (62.5%)	69 (56.6%)	
Race	Black	39 (92.9%)	36 (90.0%)	37 (92.5%)	112 (91.8%)	0.676
	Coloured	3 (7.1%)	2 (5.0%)	2 (5.0%)	7 (5.7%)	
	White	0 (0.0%)	2 (5.0%)	1 (2.5%)	3 (2.5%)	
Age, years	Mean ±SD	44.21 ±16.88	43.08 ±13.49	43.83 ±18.08	43.71 ±16.15	0.950

2.3.2 CLINICAL PRESENTATION/ EPILEPSY CHARACTERISTICS

2.3.2.1 ETIOLOGY

The majority of patients, 84 (68.9%), were already diagnosed with epilepsy whereas 38 (31.1%) presented with new onset, unprovoked, seizures (p-value= 0.002). The mean age of onset of epilepsy was 32.09 (±21.72) years.

The most common aetiology for the epilepsy was cryptogenic in all three patient groups while post ischemia was the commonest cause of epilepsy in 25% of patients who presented in status epilepticus (p Value=0.05) (Figure 2.1).

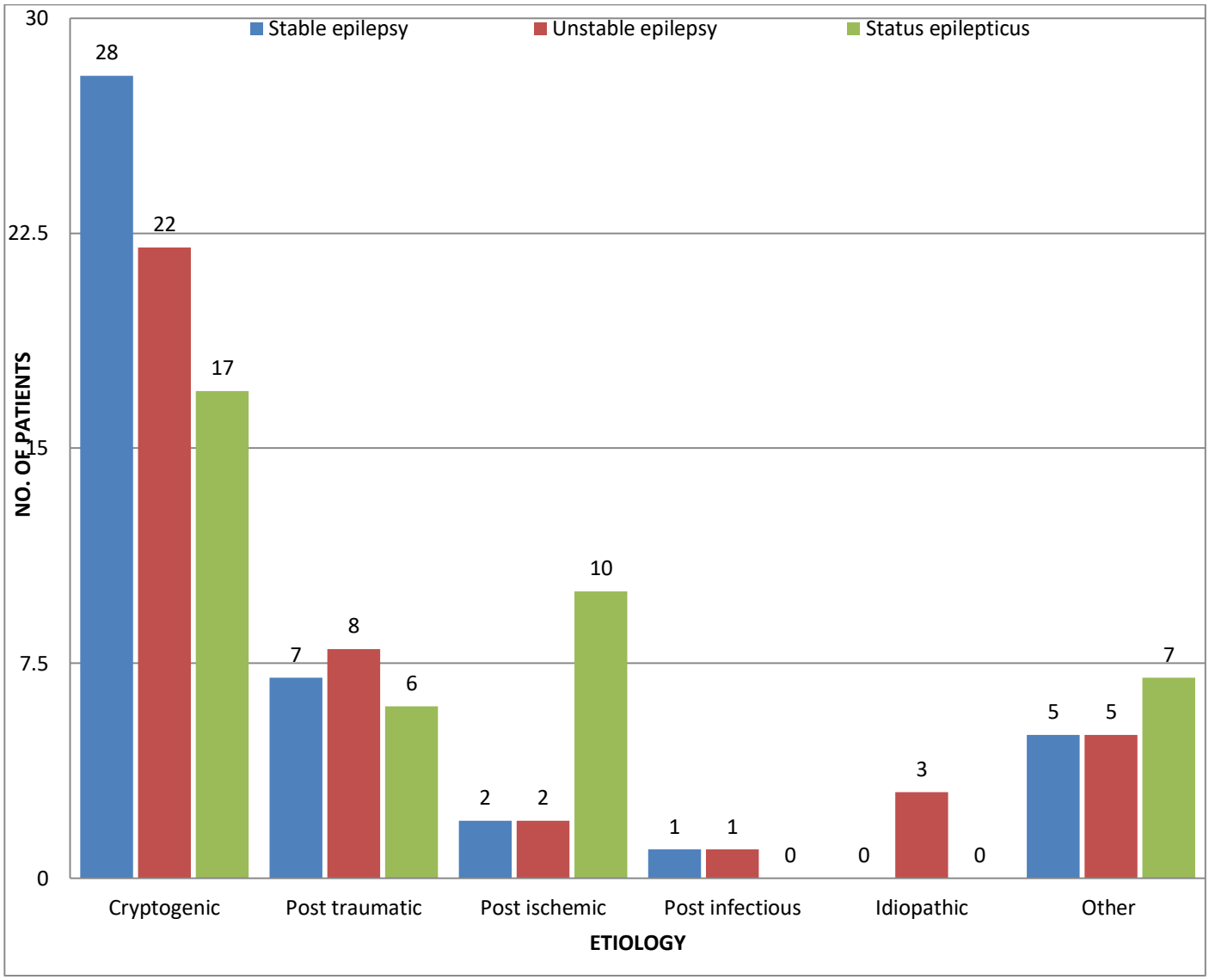

Figure 2.1: Causes of epileptic seizures

2.3.2.1 TYPES OF SEIZURES

The seizures presentations were classified according to the ILAE 2017 seizure classification into generalized tonic-clonic (GTC), partial, partial with secondary generalization and undefined. The

most common seizure types were GTC seizures. There was no significant difference by group for all the different types of seizures (Figure 2.2).

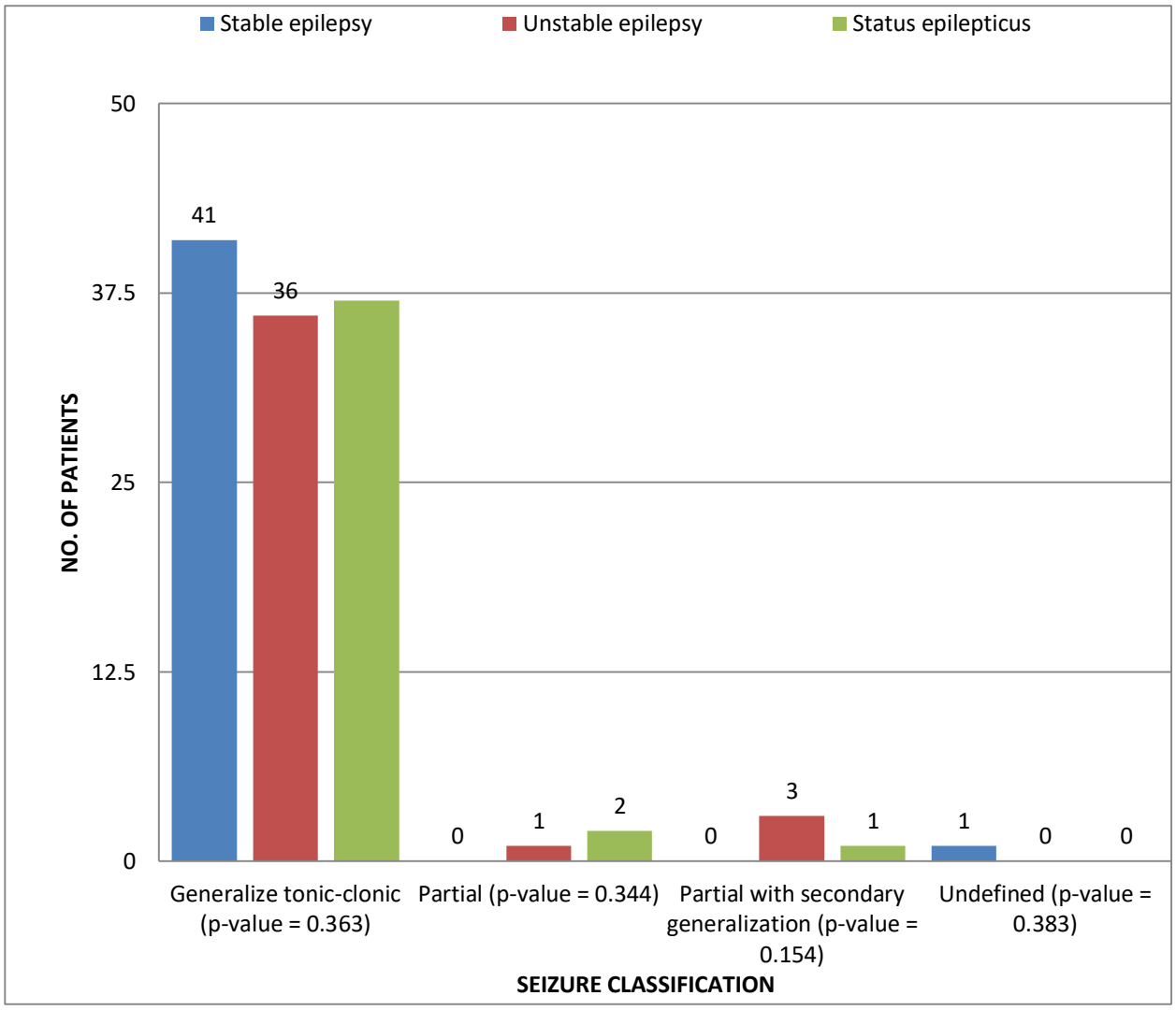

Figure 2.2: Classification of seizures

2.3.3 ANTIEPILEPTIC DRUGS

The most commonly used antiepileptic drug in this cohort was sodium valproate. 62 (50.8%) patients were being managed on a single antiepileptic drug, 54 (44.2%) on two or three drugs

while 6 (5.9%) patients had either stopped or not yet started any antiepileptic medication. There were no significant differences in the use of the medication by group, except Lamotrigine which was being used by 8 (20%) patients in the unstable epilepsy group and 9 (22.5%) in the status epilepticus group as opposed to 1 patient (2.4%) in the stable epilepsy group. These differences were significant at 5% significance level (p Value = 0.019). It can be noted that none of the patients in the stable group were on Leviteracetum, compared to 1 (2.5%) among the unstable epilepsy patients and 6 (15%) among those in the status epilepticus group. These differences were significant (p Value = 0.008) (Figure 2.3).

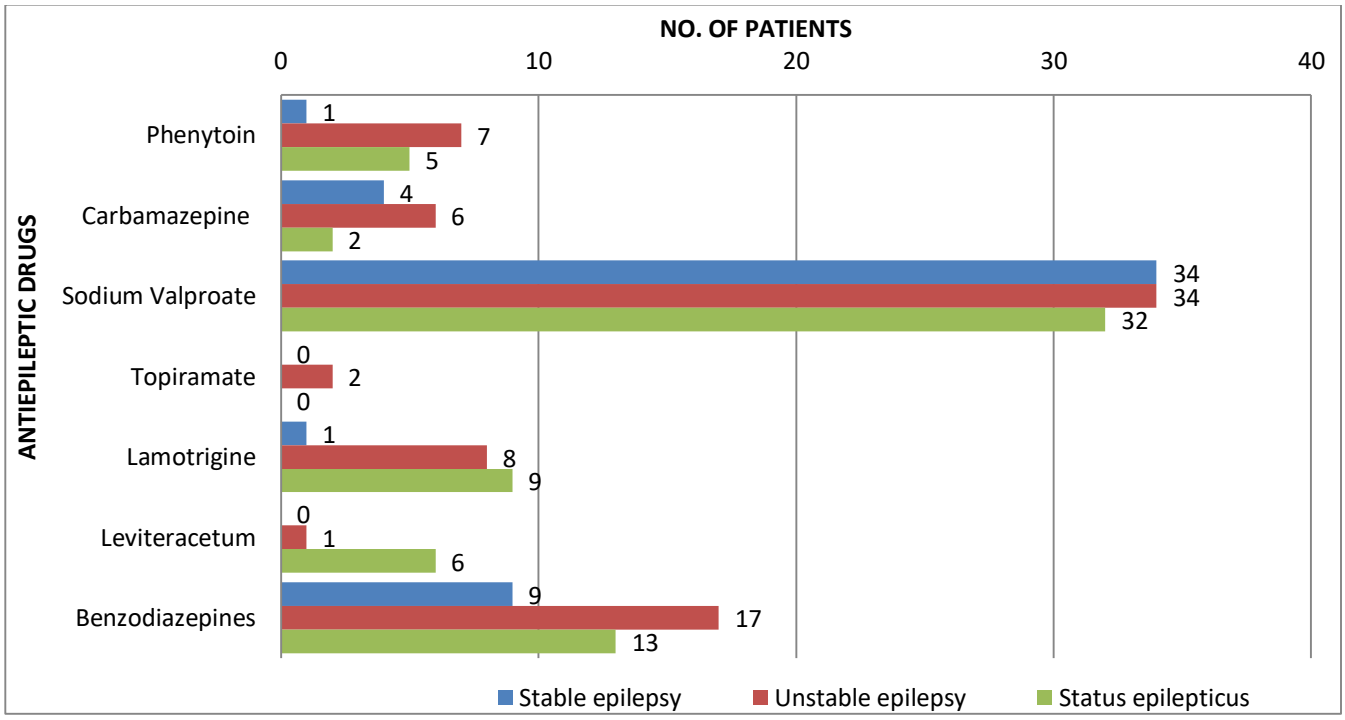

Figure 2.3: Antiepileptic drug usage

2.3.4 CARDIAC TROPONIN-T (cTnT) LEVELS

The cTnT levels were drawn on average at 24.9 h for status epilepticus group compared to an average of 50.5 h for the stable and 64.4 h for the unstable epilepsy group (p-value< 0.001). The mean cTnT was 11.36ng/L (range: 3.00-104.00ng/L). Two patients had cTnT levels above 100ng/L which is a value used to rule-in acute coronary syndrome (ACS) according to WHO rule-in level (Eisenman, A. 2006). Cardiovascular risk factors included diabetes mellitus in 11 patients, hypertension in 26 patients, dyslipidemia in 6 patients and smoking in 35 patients.

Factors such as age of onset of seizures, new or previously diagnosed epilepsy, type or cause of seizures and antiepileptic drug treatment were not shown to have significant association with the cTnT elevation. A significant proportion of the patients lacked EEG (81.1%) and imaging results (33.6%) which made it difficult to make a meaningful interpretation.

Elevated cardiac troponin-T levels

Twenty-four patients (19.6%) had elevated cTnT levels (mean = 35.6 ng/L, range: 16-104 ng/L). Fifteen (62.5%) of those had presented in status epilepticus. Fifty percent of the patients with elevated cTnT had abnormal creatinine. Patients with elevated cTnT were significantly older, with a mean age of 54.9 years (range: 20-85 years), compared to those with normal levels with a mean age of 39.9 years (range: 18-73 years) p-value <0.001 (Figure 2.4).

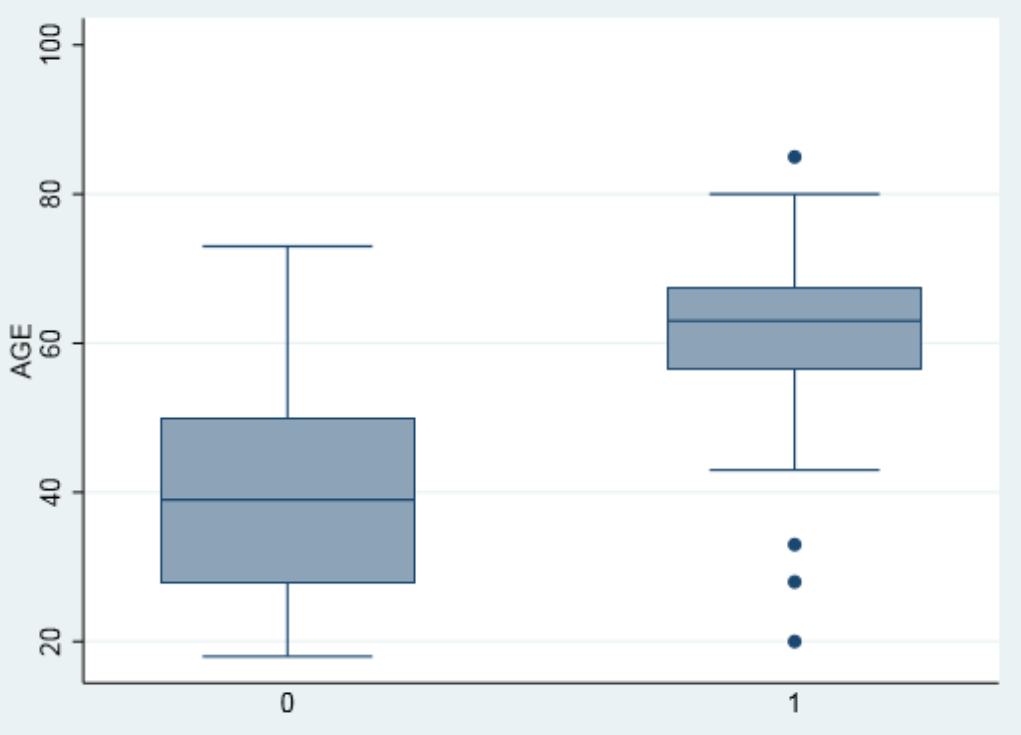

Figure 2.4: Box plot comparing the mean age (±SD) in patients with normal (0) versus elevated (1) cTnT levels.

Hypertension and diabetes mellitus were significantly more frequent in patients with elevated cTnT compared to those with normal levels. Smoking and hyperlipidemia were more common in patients with normal cTnT levels (Table 2.2).

Table 2.2: Frequency of cardiovascular risk factors in elevated versus those with normal cTnT levels.

Risk Factor	Elevated cTnT	Normal cTnT	P (Fisher's test)	95% CI
Diabetes Mellitus	7 (63.6%)	4 (36.4%)	0.001	2.55- 36.68
Hypertension	13 (52.0%)	12 (48.0%)	<0.001	2.43- 17.60
Smoking	6 (17.1%)	29 (82.9%)	0.656	0.29- 2.20
Hyperlipidemia	0 (0.0%)	6 (100.0%)	-	-

Cardiac troponin-T levels in the elderly

Twenty-six patients, 15 male and 11 female patients, were 60 years and older (mean age 66.6 years, range: 60-85 years). Of those, seventeen (65%) had elevated cTnT levels. There was no significant difference in the age of patients with high cTnT levels (mean: 67.7 years, range: 61-85 years) compared to those with normal levels (mean: 64.6 years, range 60-73 years).

Eleven patients with elevated cTnT were hypertensive, 6 diabetic, 5 smokers and none had hyperlipidemia. On the other hand, of the nine patients with normal cTnT levels, 3 were hypertensive, 1 diabetic and 5 were smokers. None had hyperlipidemia.

2.4 DISCUSSION

The mean age of our cohort was 43.7 years. Patients with elevated cTnT were of mean age 54.9 years. Sixty-five percent of our patients aged 60 years and above, were found to have elevated cTnT levels. This is consistent with a previous study that found that age is an important and consistent risk factor to develop cardiac troponin elevation (Nass et al., 2017). Fawaz et al. (2014) also found elevated cTnT levels in older patients. They make the assumption that elderly patients are more prone to demand ischemia as compared to younger patients. This was in the setting of seizures with the associated apnea, tachycardia and increased blood pressure and a resultant increase in myocardial oxygen consumption.

Cardiovascular risks factors i.e. hypertension, diabetes mellitus, hyperlipidemia and smoking, have been shown to be associated with elevated cardiac troponins in patients with seizures

(Fawaz et al., 2014; Montepietra et al., 2009; Sieweke et al., 2012). In our study, hypertension and diabetes mellitus were shown to be significant risk factors associated with elevated cTnT levels. However, in contrast to these older reports, smoking and hyperlipidemia were not significant association factors with cTnT elevation in our study.

The literature on cardiac troponin levels following seizures is not uniform with normal levels documented in patients with uncomplicated seizures, children and patients with normal cardiovascular systems (Alehan et al., 2009; Hasjagedi et al., 2009; Woodruff et al., 2003). Elevated levels were found in patients with complicated seizures (Khattab et al., 2014; Parvulesco-Codrea et al., 2006)

Thirty-seven and a half percent of the patients who presented in status epilepticus in our cohort were found to have elevated cTnT levels. They made up 62.5% of the cohort with elevated cTnT levels. This is in keeping with El Amrousy et al. (2017) who found elevated cTnI in pediatric patients with convulsive status epilepticus and concluded that elevated troponins in their patient group with no cardiovascular risk factors meant there was a myocardial oxygen supply and demand mismatch that caused cardiac ischemia.

Hocker et al. (2013) also found that markers of cardiac injury are present in nearly two thirds of patients with refractory status epilepticus. Their cohort was made up of 35 adult patients with refractory status epilepticus. A wide range of manifestations of cardiac injury, including cardiac troponin-T elevations, transient systolic dysfunction and ECG changes such as QTc prolongation, transient T-wave inversion, ST changes were also demonstrated in this study. They concluded that markers of cardiac injury in refractory status epilepticus are common and may be under recognized. In contrast, Mehrpour et al. (2013), in a study of 30 patients, of mean age 39, 1

years, with status epilepticus, demonstrated normal cTnI levels in all their patients. Their patients had normal cardiovascular profiles and they summized that in status epilepticus patients who have no underlying comorbid cardiovascular disease, cardiac troponin is not elevated.

2.5 LIMITATIONS

There has been no standardized times for collection of blood samples for the cTnT levels. Patients who presented in status epilepticus had their blood sampled significantly earlier than patients in the stable and unstable groups. This could have a bearing on the results and underestimate the true frequency of elevate cTnT levels because although cardiac troponins remain elevated for 7-14 days following myocardial injury, peak levels occur at 12-48 hours following myocardial injury (Al-Otaiby et al., 2011; Eskandarian et al., 2011; Marini et al., 2013).

We had no repeat cTnT levels, to report on temporal trends, and no cardiac investigations such as ECG, echocardiogram or coronary angiography, in patients who were found to have elevated cTnT levels, to test the significance of the elevated levels.

There was also no long term follow up on patients with elevated cTnT levels, to detect further adverse outcomes.

2.6 FUTURE STUDIES

Future research should look at testing the clinical significance of elevated cTnT levels in patients with epilepsy by way of longitudinal cTnT testing, ECG, echocardiogram and/or coronary

angiography, especially in elderly patients, patients with complicated epilepsy and those with cardiovascular risk factors.

2.7 CONCLUSION

This study demonstrates that some patients have elevated cTnT levels following a seizure. This subgroup of patients was significantly older in age, had presented with complicated epilepsy i.e. status epilepticus, and had cardiovascular risk factors, hypertension and diabetes.

Cardiac troponins are more sensitive markers of subtle myocardial injury than ECG or echocardiogram (Fawaz et al., 2014), however, in our study, a lack of further testing, by way of repeat cTnT levels, ECG and echocardiogram, of the patients with elevated cTnT levels, means that the significance of the elevated cTnT levels is unclear.

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APPENDIX I:

DATA COLLECTION SHEET

DEMOGRAPHICS

Study Number: Date:

Age (years): | | |

Sex: | M | F |

Race: | B | W | C | I | A |

Telephone Number: …….

PRESENTATION

New onset seizure: | Y | N |

Known with epilepsy: | Y | N |

Age at first seizure (years): | | |

Elapsed time since the last seizure (hours): | | | |

Average number of seizures/ week over the last 4 weeks: | | |

Cause:

Cryptogenic	Y	N
Post traumatic	Y	N
Post ischemic	Y	N
Post infectious	Y	N
Idiopathic/ genetic	Y	N
Other lesions	Y	N

Type of seizure:

Generalized tonic-clonic	Y	N
Partial	Y	N
Partial with secondary generalization	Y	N
Undefined	Y	N

Convulsive status epilepticus:

Y	N

Antiepileptic drugs used:

Number of drugs currently used:

Name and dosages:

AED	Current use	Previously used (past 12 months)	Never used	Dose(mg)
Phenytoin				
Phenorbarb				
Carbamazepine				
Na-valproate				
Topiramate				
Lamotrigine				
Leviteracetum				
Other				

Chronic medical conditions:

Hypertension	Y	N
Diabetes	Y	N
Hyperlipidemia	Y	N
Other	Y	N

Smoking:

Y	N

Alcohol

Y	N

NEUROLOGY EXAMINATION

N	Abn

INVESTIGATIONS

Laboratory:

Serum cardiac troponin-T level:

N	Abn

Creatinine:

N	Abn

Biochemistry:

N	Abn

Imaging Brain CT/ MRI:

N	Abn	n/a

EEG:

N	Abn	n/a

APPENDIX II: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr DSA Makwela

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180979

NAME: (Principal Investigator)	Dr DSA Makwela
DEPARTMENT:	School of Clinical Medicine Division of Neurology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Serum levels of cardiac troponin-T in adult patients with epilepsy
DATE CONSIDERED:	28/09/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor G Modi
APPROVED BY:	Dr N Naran, Deputy Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/01/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in September and will therefore reports and re-certification will be due early in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX III: PERMISSION TO CONDUCT RESEARCH (CMJAH)

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email:Nobwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
7th November 2018

Dear Dr D. Makwela

STUDY TITLE: Serum Levels of Cardiac Troponin T in Adult Patients Epilepsy

Permission to review patient file for the above mentioned case report is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

~~Supported~~ / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 7/11/2018

Approved / ~~not approved~~

Ms. G. Bogoshi
Chief Executive Officer
DATE: 07/11/2018

APPENDIX IV: PERMISSION TO CONDUCT RESEARCH (CHBAH)

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 10th December 2018

TITLE OF PROJECT:

Serum levels of cardiac troponin-T in adult patients with epilepsy.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr D Makwela

Department: Neurology

Supervisor : Prof G Modi

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 10/12/2018

Approved/Not Approved
Hospital Management
Date: 13 12 2018

APPENDIX V: PERMISSION TO CONDUCT RESEARCH (HJH)

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries; Dr. M.R. Billa
Chief Executive Officer
Tel :(011) 489-0306/1087
Fax :(011) 726-5425
E mail: Raymond.Billa@gauteng.gov.za
Date: 27 November 2018

Dr.M.R.Billa
Chief Executive Officer
Helen Joseph Hospital

Dear Dr. M.R Billa

STUDY: Serum level of cardiac troponin T and I in adults patients with uncontrolled epilepsy

RESEARCHERS: Dr O. Makwela

Ethics:M180979

Above the study was discussed at the Research Committee meeting. We recommend that permission be granted for Helen Joseph Hospital to be used as a site for the above research, However , since this is individual /Patients.
Upon completion of the study, copy thereof should be submitted to Helen Joseph Hospital.
It is duty of the researcher to collect the data to the relevant department after the Research Committee approved the study.

Thank you

Dr. Murimisi Mukansi
CHAIRPERSON
DATE:

Approved

Dr. M.R. BILLA
CHIEF EXECUTIVE OFFICER
DATE: 28-11-2018

APPENDIX VI: PLAGIARISM REPORT

783007:mmed_report.docx

ORIGINALITY REPORT

13%	7%	16%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Ahmad Fawaz, Wassim Nasreddine, Yamane Makke, Samir Atweh, Jaafar Wazne, Maher Arabi, Ahmad Beydoun. "Association of cardiovascular risk factors and troponin elevation after generalized tonic-clonic seizures", Seizure, 2014 Publication	3%
2	Mohammed A. Al-Otaiby, Hussein S. Al-Amri, Abdulrahman M. Al-Moghairi. "The clinical significance of cardiac troponins in medical practice", Journal of the Saudi Heart Association, 2011 Publication	2%
3	Mariana B. Nejm, Francisco Sandro Menezes-Rodrigues, Luciana de Paula, Marcia J.G. Marques et al. "Serum levels of cardiac troponin I and sudden unexpected death in epilepsy: How much, how often, and when?", Epilepsy & Behavior, 2016 Publication	1%

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7	Anastasios Chatzikonstantinou, Anne D. Ebert, Michael G. Hennerici. "Temporal seizure focus and status epilepticus are associated with high-sensitive troponin I elevation after epileptic seizures", Epilepsy Research, 2015 Publication	1%
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12	Bermeo-Ovalle, Adriana C., Jeffrey D. Kennedy, and Stephan U. Schuele. "Cardiac and Autonomic Mechanisms Contributing to SUDEP	1%

:", Journal of Clinical Neurophysiology, 2015.
Publication

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