DIAGNOSTIC PERFORMANCE OF THE AMBULATORY EEG VERSUS ROUTINE EEG AND RISK FACTORS FOR SEIZURE RECURRENCE AMONG INDIVIDUALS WITH FIRST SINGLE UNPROVOKED SEIZURES

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Abstract

Background and objectives: Routine electroencephalography (rEEG) remains central in the prognosis of seizure recurrence among individuals with a First Single Unprovoked seizure (FSUS). Furthermore, it is well-established that the presence of epileptiform discharge (ED) in the EEG increases the risk of further seizures among individuals with FSUS up to 3 times compared with individuals without such EEG changes. However, the rEEG has low sensitivity, leaving patients and clinicians without a fast and accurate tool for the prognosis of further seizures. This study aims to determine and compare the discriminative power, clinical predictive value, and global diagnostic accuracy of the ambulatory EEG compared with the first rEEG and second rEEG. This study also aims to determine risk factors for further seizures among individuals with FSUS, including ED in the ambulatory EEG.

Methods: The study used a prospective cohort design with a total of 100 individuals with FSUS who underwent three modalities of EEG (first rEEG, second rEEG and Ambulatory EEG) and who were followed up for one year period. All the required information was available in this dataset, and further seizures were prospectively recorded. The three EEG (first, second rEEGs and ambulatory EEG) were interpreted by licensed neurologists recognized by the Royal College of Physicians and Surgeons of Canada and fully accredited by the Canadian Society of Clinical Neurophysiologists. Diagnosis of epilepsy was made based on clinical, neurophysiology and imaging tests following the definition of epilepsy by the International League Against Epilepsy 2014. Receiver-operating-characteristic (ROC) analysis was used to evaluate the results. Also, table-life and survival analysis were used to determine the risk for further seizures during the 52 weeks follow-up period.

Results: We found that the ambulatory EEG's diagnostic accuracy was better than the first and second EEG (0.79 vs. 0.51 and 0.54, respectively) in the population. Age group was a confounder in the association between seizure recurrence at 52 weeks and the presence of ED in the ambulatory EEG. The presence of ED in the ambulatory EEG increased the risk of seizure recurrence among individuals with FSUS 3.2 times when adjusted for use of antiseizure medication (ASM) and age group. Finally, other risk factors modifying the association between further seizures and the presence of ED in the ambulatory EEG included age group of >60 years (HR: 0.27 95%CI: 0.10,0.74) and the use of ASM (HR: 12.9, 95%CI: 5.6, 29.3).

Conclusions: The overall diagnostic accuracy of the ambulatory EEG as a means of detecting ED among individuals with FSUS is better than the first and second rEEG. Furthermore, ED in the ambulatory EEG is a significant risk factor predicting further seizures after a single unprovoked seizure after adjusting for the use of ASM and age group.

Significance: This study advanced our knowledge about the use of ambulatory EEG as an ancillary tool for predicting further seizures after FSUS and established that the presence of epileptiform activity in the ambulatory EEG is a risk factor for further seizures after adjusting for use of ASM and age group. The use of ambulatory EEG may reduce diagnostic errors and is also low-cost and better tool which can be used worldwide for more accurate diagnosis of epilepsy compared to rEEG.

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The Author

Lizbeth Hernandez Ronquillo

Dedication

This thesis is dedicated to:

- To God for taking care of my family and me through good times and bad times.
- In memory of my husband Jose Francisco Tellez Zenteno in heaven, the only man in my life who taught me to be humble, patient, and positive.
- To my children, Guillermo and Isabelle Tellez-Hernandez, without whom this thesis would have been completed many years earlier. I added to the role of mother the competing demands of work, study and personal development; I hope one day you may understand.
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Pages

Table of contents

List of Tables

Pages

List of Figures

pages

List of abbreviations

ASM	Antiseizure medication
CI	Confidence Interval
CNS	Central Nervus System
EEG	Electroencephalogram
ER	Emergency Room
ED	Epileptiform Discharges
FSUS	First Single Unprovoked Seizure
GTCS	Generalized Tonic-Clonic Seizures
ILAE	International League Against Epilepsy
LR	Likelihood Ratios
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
OR	Odds Ratio
PNES	Psychogenic Non-Epileptic Seizures
PPV	Positive Predictive Value
RR	Rate Ratio
rEEG	Routine EEG

SK	Saskatchewan
SN	Sensitivity
SP	Specificity
SSC	Single Seizure Clinic
SUS	Single Unprovoked Seizure
YRS	Years

CHAPTER 1: INTRODUCTION

1.1 Background

Unprovoked epileptic seizures are common, affecting approximately 8% of the population in their lifetime. However, only 30% of the patients who present with a first single unprovoked seizure (FSUS) will have a seizure recurrence (i.e., epilepsy) in the next one to two years (1).

The FSUS is a powerful event for patients with profound life-altering effects such as a driver's license restriction, unemployment, injuries, and accidents. Furthermore, the uncertainty about the seizure recurrence carries a significant social and psychological burden for patients and their families.

For the physician evaluating patients with SUS, this situation merits close scrutiny as he/she must decide if the SUS was a truly epileptic seizure or not or whether the patient is at high risk for seizure recurrence or not, and must ultimately establish the diagnosis of epilepsy and initiate treatment with antiseizure medication (ASM), or not (2).

To establish the diagnosis of SUS, the physician must start with a rigorous clinical evaluation emphasizing conventional risk factors for seizure recurrence such as a family history of seizures, personal account of febrile seizures, head trauma and brain infections, among others. The American Academy of Neurology and American Epilepsy Society guidelines 2015 also recommend the use of tools such as Magnetic Resonance Imaging (MRI) and routine electroencephalogram (EEG) (3).

The routine EEG is a neurophysiological test proven beneficial in the prognostic determination of the likely seizure recurrence. If abnormalities on the routine EEG are found, the risk of seizure recurrence increases 2.1 times. However, the routine EEG has its limitations, as its accuracy to detect abnormalities after a first unprovoked seizure only has a sensitivity of 17% and specificity of 95% (4). Previous studies have shown that some factors improve the accuracy of

finding epileptiform discharges (ED) in the routine EEG (rEEG) in single unprovoked seizures (SUS), such as early recording (up to 72hrs) relative to the index event. Also crucial in increased accuracy of the EEG is the inclusion of sleep deprivation, the use of serial EEG studies, and prolonged recordings (5).

Ambulatory EEG is a monitoring modality that allows the recording of continuous EEG for 24 hours at home, including the patient's sleep cycle (6). The use of ambulatory EEG has resulted in a higher rate of detection of abnormalities compared with the rEEG (6).

Only one study compares the ambulatory EEG with an EEG using sleep deprivation in detecting epileptiform discharges in patients with single unprovoked seizures (7). In this study, the authors examined a group of patients receiving only an ambulatory EEG and compared their outcomes with another group of patients receiving a sleep-deprived EEG. After a year following the FSUS, the diagnosis of epilepsy was made. The authors concluded that the diagnostic accuracy was similar between both modalities. However, the methodology had flaws as it was a retrospective study, and the two tests were performed in different subjects who may not have been fully comparable. Therefore, a study evaluating the ambulatory EEG in patients with single unprovoked seizures and its relationship with recurrence is needed.

1.2 Statement of the problem

On average, 1 in 10 people will have a single epileptic seizure in their lifetime. Furthermore, the presence of a single epileptic seizure has a profound physical, socio-economical, and psychological impact on an individual and his/her family. The challenges for the attending clinician are to find the possible etiology of the seizure and forecast the recurrance risk with the use of clinical evaluation and diagnostic tools such as a routine EEG, which with the presence of epileptiform discharges (ED), either interictal or ictal, are one of the main predictors for recurrance

of seizures (3). While highly specific, the routine EEG's sensitivity to detect ED after FSUS ranges between 17 to 23% (4,8). An evaluation of ambulatory EEG for the detection of ED and prognostic was developed to respond to the need for a better diagnostic and prognostic tool to assess patients presenting with FSUS. The ambulatory EEG has shown an excellent diagnostic yield for diagnosing, classifying and managing individuals with epilepsy (9). However, there is limited evaluation of the ambulatory EEG in the setting of FSUS. Therefore, a rigorous study evaluating the ambulatory EEG in patients with FSUSs and its relationship with recurrence is needed.

1.3 Purposes

The first main purpose of this study was to estimate the discriminative power (sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and clinical predictive value (Likelihood Ratios (LR)) of the ambulatory EEG, the first routine EEG (rEEG), and a second rEEG to detect epileptiform discharges (ED) in adult patients with a first single unprovoked seizure (FSUS) who present to the Single Seizure Clinic at Royal University Hospital in Saskatoon, SK. Canada. This purpose also included the comparison of the internal validities within the three modalities of EEGs.

The second primary purpose of this study was to estimate the risk factors of further seizures after FSUS and define the ambulatory EEG's utility in predicting seizure recurrence after one-year follow-up.

Improving the accuracy of ED detection and evaluating seizure recurrence with the ambulatory EEG in patients with a FSUS will assist the physician in initiating timely and accurate treatment and decreasing the uncertainty, adverse social effects, and ultimately harm for these vulnerable patients.

1.4 Research questions and hypotheses

This study investigated the following four research questions and respective hypotheses.

1.4.1 Question 1

What is the discriminative power (sensitivity, specificity, PPV, NPV) and the clinical predictive value (LR) of the ambulatory EEG for detecting ED in individuals presenting with a FSUS at the Single Seizure Clinic (SSC) at Royal University Hospital in Saskatoon, SK, Canada.

Hypothesis: The ambulatory EEG's discriminative power to detect ED in patients who present with FSUS will be comparable to measures reported in the literature for ambulatory EEG and epilepsy (within the range of 75-80%).

1.4.2 Question 2

Is there better discriminative power and clinical predictive value of ambulatory EEG than first and second routine EEGs (rEEGs) in patients presenting with a FSUS?

Hypothesis: The sensitivity, PPV, and LR for detecting an ED will be better with ambulatory EEG in patients presenting with a FSUS than the first rEEG and second rEEG.

1.4.3 Question 3

What are the variables associated with seizure recurrence at 52 weeks (one year) of follow-up in patients that present with a FSUS?

Hypothesis: The likelihood of seizure recurrence after 52 weeks (one year) of follow-up in a patient that presents with a FSUS will likely be approximately more than 50%. Also crucial to one-year seizure recurrence will be age, history of brain lesions, stroke and psychiatric comorbidity, presence of nocturnal seizures, and MRI or CT abnormalities.

1.4.4 Question 4

Is the presence of ED in the ambulatory EEG a risk factor for seizure recurrence during 52 weeks (one-year) follow-up after a FSUS?

Hypothesis: The presence of ED in the ambulatory EEG will be a predictor of seizure recurrence within a year's follow-up.

1. 5 Organization of this Thesis

The content of this thesis is organized into six chapters.

- Chapter 1- The introduction sets the stage for the current evaluation of the first Single Unprovoked Seizure together with its evaluation tools. The BACKGROUND segment offers a general view of the definition of FSUS and briefly summarizes the problems with the current diagnostic test used. STATEMENT OF THE PROBLEM identifies the problem with the present use of the routine EEG in assessing the FSUS. PURPOSE describes concisely what this research is trying to achieve, laying out in RESEARCH QUESTIONS more specifically our questions of interest.
- Chapter 2-The review further examines the definitions of FSUS (OVERVIEW), the EPIDEMIOLOGY and PROGNOSTIC OUTCOME of the FSUS. This chapter also describes the current state of the diagnostic approach to the FSUS and the advantages and disadvantages of the use of different modalities of the electroencephalogram EEG.
- Chapter 3-Theoretical Perspectives introduce the three fundamental theories that guide this research: CLINIMETRICS, DIAGNOSTIC ERROR and VALIDITY THEORY.

- Chapter 4- METHODS presents particular procedures that were undertaken in this research. In the STUDY DESIGN, we describe the STUDY POPULATION where the cohort originated, the process whereby patients were invited to the study, the standard protocol in the evaluation of FSUS (SEIZURE PROTOCOL and CLINICAL DIAGNOSIS) and the use of the gold standard (EEG) as well as the interventions (second EEG and Ambulatory EEG) to be compared. In this chapter we also present the inclusion, exclusion criteria, and the outcomes measured. Lastly, the ETHICAL CONSIDERATIONS and the ANALYSIS performed for each purpose were described.
- Chapter 5-Results, presents the findings of the study based upon the information gathered after the use of the methodology in Chapter 4. In the POPULATION, we describe the cohort obtained followed by the times between each study (WATING TIMES) and the DESCRIMINATIVE POWER and CLINICAL PREDICTIVE results VALUE of diagnostic tests. Finally, in this chapter, the results of the SEIZURE RECURRENCE AND ASSOCIATED RISK FACTORS, tables and figures were added.
- Chapter 6- Discussion, conclusions and recommendations present the results compared with previous studies in EEG and seizure recurrence after FSUS. It concludes how these findings will impact the current evaluation of FSUS all over the world.

CHAPTER 2: LITERATURE REVIEW

2.1 First epileptic seizure: an overview

An epileptic seizure is a “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (10). Epileptic seizures are further classified as provoked and unprovoked seizures. Provoked seizures are the result of an insult or metabolic or toxic disturbance of the brain. Some factors that may precipitate provoked seizures include fever, acute traumatic brain injury, excessive alcohol intake, withdrawal from alcohol and drugs, hypoglycemia, electrolyte disturbances, acute CNS infections, acute ischemic stroke, intracranial hemorrhage, and pro-convulsive drugs (such as clozapine, maprotiline, tramadol, theophylline, baclofen) (11). Furthermore, individuals experiencing a first provoked epileptic seizure are nine times more likely to die within 30 days after the presentation but are 80% less likely to present with a subsequent unprovoked seizure(12).

On the other hand, unprovoked epileptic seizures are seizures without identified proximal precipitants (13). Individuals who experience a first unprovoked epileptic seizure have a 65% higher risk of subsequent unprovoked seizures than those who present with a provoked epileptic seizure (12).

The presence of subsequent unprovoked seizures is vital due to the implications of the eventual diagnosis of epilepsy. Briefly, the diagnosis of epilepsy is based on (14)

1. At least two unprovoked seizures occurring >24 h apart.

2. One unprovoked seizure with additional features accompanied by circumstances that increase the possibility of a seizure recurrence, such as an epileptiform discharge in the

electroencephalogram (EEG) study or stroke lesion in an imaging study such as Magnetic Resonance Imaging (MRI) or Computed Tomography (CT)).

3. Diagnosis of an epilepsy syndrome such as Dravet's syndrome, childhood absence epilepsy, or juvenile myoclonic epilepsy.

The development of potential subsequent unprovoked seizures or a recent diagnosis of epilepsy has significant medical, social, and emotional consequences, most notably on immediate driving restrictions. Driving restriction is one of the most critical outcomes among adult patients, as it has a significant impact on the lifestyle, employment, and freedom of the patient and his/her family. Driving restrictions are generally imposed after the first seizure. Potential loss of consciousness during driving can result in serious risks, including death for the patients and the public (1). However, driving restrictions vary between countries and jurisdictions from no restriction to 10 years for commercial drivers (11).

Other social effects of epilepsy include unemployment, a decrease in the quality of life and stigma. Patients with a diagnosis of epilepsy also face mental health issues such as depression, anxiety, and impairment of cognition and memory (15).

For the purpose of this review, the word "seizure" is used to indicate an epileptic seizure.

2.2 Epidemiology of the first unprovoked seizure

Information about the incidence of the first single unprovoked seizures (FSUS) in developed countries comes from studies with prolonged follow-up times. In these studies, the cumulative incidence of single and recurrent epileptic seizures by the age of 80 years is 8% (16). Based on this information, 8% of individuals in a population will experience a single unprovoked seizure during their anticipated lifetime of 80 years. Unprovoked seizures are more frequent in

men and at the extremes of ages, i.e. children less than a year of age and individuals older than 65years (16).

The diagnosis of unprovoked seizures results in an increase in mortality among young children and the elderly compared to the general population (16).

2.3 Prognostic outcome of a first unprovoked seizure

Since the presence of a second unprovoked seizure is essential for the diagnosis of epilepsy, accurate knowledge about the risk of recurrent seizures after a FSUS is critical. In general, the risk of recurrent seizures in adults in the two years following the diagnosis of FSUS is between 21% and 45%. However, this percentage changes with age at diagnosis. In the pediatric population, the risk of the seizure recurrence is between 37 and 60% in the first three years following the FSUS (17). Meanwhile, in elderly patients, the likelihood of a second seizure one year after FSUS is between 45 and 62%.(18). Recurrences generally occur in the six months following a first seizure in 50% of patients and by two years in 80% of patients (19–21).

Because of the possibility, but not certainty, of seizure recurrence, the main clinical decision is whether to treat or not treat patients presenting with a FSUS to avoid future seizures. This question has been addressed by randomized clinical trials which have included children and adults, showing that although the treatment with antiseizure medication (ASM) reduces recurrences, the use of ASM does not change long-term outcomes (22–25).

2.3 Current diagnostic approach for patients presenting with a FSUS

The main objective of assessing patients with FSUS is to establish an accurate and timely diagnosis (26). In particular, evaluating the likelihood of seizure recurrence is one of the most

critical factors that will lead to evidence-based treatment decisions (27), potentially avoiding unnecessary stress and treatment with ASM.

The typical patient who presents with a FSUS and seeks medical attention has suffered a generalized tonic-clonic seizure or focal onset seizure with secondary generalization (20). The clinical approach to these patients includes careful evaluation with differential diagnosis incorporating diagnostic test studies. As the approach and symptomatology of patients with FSUS among children differ from those in the adult population, the following review is based on the adults and the elderly.

In the adult population, the clinical evaluation initially includes confirming the epileptic nature of the event through history and physical examination (28). In the gathering of the history, it is vital to recognize and search for predisposing factors such as family history of seizures or epilepsy, cognitive and developmental deficits, history of conventional risk factors such as a history of brain injury, stroke, Central Nervous System (CNS) infections, febrile seizures; and triggers such as toxins, sleep deprivation, flashing lights, and hyperventilation. The clinician must also take a detailed survey of signs and symptoms previous to the event such as aura (vision of lights or colour, epigastric rising sensation), behavioural changes (behavioural arrest, unresponsiveness or period of confusion), automatisms (pill-rolling, picking, lip-smacking), tiredness, and irritability (28). The next step is to collect a thorough descriptive seizure history, including order of appearance and duration of every component(including the presence of nocturnal seizures), level of consciousness, motor activity (clonic, tonic, tonic-clonic), sensory abnormality, predominant side of occurrence of each component, vocal output (cries, grunts) stereotypical facial expression (facial slackening, eyelid fluttering, staring or eye deviation) autonomic features (pallor, sweating, piloerection), incontinence, respiration pattern, fall or loss

of tone, and tongue biting (28). It is also essential to gather information about signs and symptoms after the seizures, such as sleepiness, amnesia, confusion, headache, partial paralysis, muscular pain, behavioural changes, and injuries secondary to the seizure episode (28).

Based on data from diverse, prospective studies, the presence of primary brain lesions or insults causing seizures (remote symptomatic etiology) and the presence of nocturnal seizures have been found to increase seizure recurrence from 2.5 to 2.1 times for at 1 to 5 years respectively, following the presence of FSUS (29). Among the differential diagnoses that have to be considered are syncope, psychogenic nonepileptic events, hyperventilation, migraine, panic attack, transient global amnesia, and transient ischemic attack (30).

Standard evaluation of adults with FSUS includes the use of medical imaging such as 1.5 Teslas Magnetic resonance imaging (MRI) and Computed tomography (CT) scan. There is consistent evidence showing that the seizure recurrence is higher in patients with significant MRI lesions like dysplasias, leukomalacia/gliosis, encephalomalacia, any gray matter lesion, mass lesion, hemorrhage, vascular lesion, hippocampal abnormality, ventricular enlargement greater than 1.5 cm, or prominence of extra-axial fluid spaces greater than 1.0 cm (3,29,31). However, only 10% of the patients with SUS have CT or MRI lesions (3).

2.4. The electroencephalogram as a diagnostic test in the assessment of a patient presenting with FSUS

The gold standard of neurophysiology studies used in evaluating a patient with SUS is the electroencephalogram (EEG). The American Academy of Neurology recommends using EEG in children and adults after the presence of a FSUS based on evidence that the presence of epileptiform abnormalities will double the risk of seizure recurrence (3). Furthermore, the most recent operational definitions of epilepsy propose that the diagnosis of epilepsy can be made after

a SUS if there is evidence to suggest that the risk of recurrence is higher than 60% (32), and the presence of ED in the rEEG increases the risk of further seizure by 60%.

The rEEG in the assessment of patients with FSUS may help for several reasons. Firstly, EEG abnormalities contribute to characterized seizure type and potential epilepsy syndrome. Secondly, in specific cases, the EEG may detect subtle seizures, including absence, myoclonic, or partial seizures. Thirdly, specific EEG patterns may detect the presence of a focal cerebral lesion. Lastly and most importantly (33), the detection of Epileptiform Discharge (ED) is predictive of seizure recurrence (31).

However, there are differences in opinions about the effect of timing, frequency, use of specific techniques such as sleep deprivation, and length of EEG on the increased likelihood of finding ED on the EEG.

In general, the research on the role of EEG on the seizure recurrence on FSUS has been based on routine EEG within 2 to 10 days after FSUS (34–36).

The routine EEG is a brief (usually 20-40 minutes) and noninvasive test that records the brain's spontaneous electrical activity through scalp electrodes attached to a recording machine (37). These electrodes are placed by trained technologists using international standards. Some technical requirements to ensure a good quality clinical EEG recording must be satisfied (37). These requirements include electrode type, electrode placement, electrode impedance, number of recording channels, montages, sensitivity, filters, calibration, paper speed, length of the recording, hyperventilation, and photic stimulation (37).

The EEG has been used since 1875 when the English physician named Richard Caton demonstrated his recording of electrical impulses in an animal’s exposed cerebral cortex. More

than one hundred years later, in 1929, German physiologist and psychiatrist Hans Berg recorded the first human EEG. In 1935, Gibbs and associates (1935) described patterns in the EEG related to epilepsy. Since then, numerous advances have occurred, ranging from multiple-channel EEG recording to digital EEG (38).

2.5 Conundrums of the routine electroencephalogram

The role of EEG on seizure recurrence has been well recognized. However, rEEG has its limitations.

A recent metaanalysis of the literature aiming to ascertain the accuracy of the rEEG after a FSUS found that in adults, the sensitivity and specificity of epileptiform discharge for seizure recurrence of rEEG were 17.3% (95%CI: 7.9, 33.8%) and 94.7% (95%CI:73.7,99.1), respectively. These results resulted in a Positive Predicted Value (PPV) of 77% and a Negative Predicted Value (NPV) of 47% (4). Although the use of EEG improves the determination of recurrence risk after a FSUS compared with only the clinical diagnosis, it is not perfect. This situation has incited the development of tools with higher sensitivity and specificity.

One factor potentially improving the ability to detect epileptiform abnormality is the timing of a routine EEG after a FSUS. The hypothesis behind this idea is that a routine EEG (rEEG) performed shortly after the seizure occurrence should provide more accurate information about EEG abnormalities. There is little research data directly comparing early and late EEG. King et al. in a prospective study assessing early EEG(within 24hrs of a seizure) and late EEG on 300 pediatric and adult patients with first seizure, found that early EEG (within 24hrs) was more useful in the diagnosis of epileptiform abnormalities than later EEG (51% vs. 34%) (39). However,

practical realities pose various logistic problems in obtaining an early EEG in emergencies and emergency rooms (ER) (5).

Another factor potentially improving the accuracy of the rEEG assessment for epileptiform activity after the FSUS is a repetition of the rEEG regardless of the timing. Salinsky et al. retrospectively reviewed 1,201 rEEGs from 429 adults with an epilepsy diagnosis. They found that abnormalities, which included ED, were observed in 50% of patients in the first EEG, 84% by the third EEG, and 92% by the fourth independent rEEG (40). Similarly, in a prospective study, Baldin et al. found that in patients with SUS, the epileptiform abnormalities were present in 39% of cases after the first rEEG and 68% of the cases after the third rEEG (41). However, the repeated rEEG approach is associated with similar problems inherent as the single rEEG, such as the length of recording and exclusion of sleep samples. Furthermore, there is insufficient evidence about the economic impact and the advantages of series of rEEG vs. one rEEG.

Another factor potentially improving the rEEG assessment's accuracy is the inclusion of sleep deprivation and the inclusion of the individual’s sleep cycle. Sleep deprivation is a method frequently used for inducing epileptiform activity in individuals with predisposition factors (37). Research has shown that the repeated EEG with the use of sleep deprivation compared with the first rEEG in individuals with the first unprovoked seizure (FSUS) increased the findings of epileptiform abnormalities from a yield of 43% to 61% (39). The problem with sleep deprivation is that this method is quite challenging to carry out, as individuals must be awake for more than 20 hrs, which might even be traumatic for some patients (37).

Finally, another factor that may affect the accuracy of the EEG is the length of the study. More extended studies are usually made with 24 hrs video EEG. Video Electro Encephalogram

(VEEG) is the synchronous recording and display of EEG patterns and video-recorded clinical behaviour. Recording of 24hrs or more is generally done in a hospital inpatient setting in the Epilepsy Monitoring Unit. VEEG is the gold standard in the identification of localization and type of seizures in patients with epilepsy. The study of the use of VEEG in FSUS by Chen et al. has shown that the presence of epileptiform discharge increases the risk of seizure recurrence by 2.8 times compared with the absence of epileptiform discharge (42). Also, Chen's study showed that of 134 patients with FSUS, 43.3% (58 patients) had normal VEEGs, and 47.7% (76 patients) had abnormal VEEGs, although, with the later abnormal group, only 73.7 % had ED abnormalities. Patients presenting with a SUS and ED on the VEEG had a 2.84 times higher increased risk of seizure recurrence (42).

In the final analysis, we may conclude that the best EEG modality to evaluate epileptiform activity in patients with FSUS is to use the EEG in the first 72hrs, with at least four EEGs after the index event, the use of EEG during sleep and finally, prolonged recording.

A modality of EEG that may combine some of the best factors in the accurate evaluation of ED in patients with FSUS, including prolonged recording (up to 96 hrs) and the inclusion of sleep cycle, is the ambulatory EEG (6). Not only is the Ambulatory EEG comparable to the inpatient VEEG, but it also results in a 65% lower cost than VEEG (6) and does not require the use of inpatient services.

The use of ambulatory EEG has been previously evaluated in patients with an established diagnosis of epilepsy and with patients presenting with FSUS.

The study by Dash et al. prospectively evaluated the yield of ambulatory EEG for diagnosis, syndromic classification, and management of epilepsy. The researchers showed that a diagnostic yield of the ambulatory EEG was 72% to confirm the diagnosis of epilepsy (9).

Another study evaluating the clinical utility of ambulatory EEG is the study of Liporace et al. In this study, the ambulatory EEG was compared with sleep-deprived EEG and a rEEG in 46 patients with a previous diagnosis of epilepsy. This study showed that the ambulatory EEG and sleep-deprived EEG improved detection of epileptiform discharges by a similar amount (24% vs. 33%). However, the ambulatory EEG detected seizures in 15% of the patients missed by the sleep-deprived EEG (43).

In 2016, Keezer et al. prospectively examined 72 individuals with diagnostic of epilepsy who were referred to the EEG laboratory as part of their regular medical care. The ambulatory EEG (23 hrs) was compared with a simultaneous rEEG, with authors reporting that the sensitivity of the ambulatory EEG was 2.23 times greater than the rEEG for ED. Furthermore, 25% of ambulatory EEG recorded epileptic seizures, which had been missed by the routine EEG (44).

2.6 Discriminative power of a diagnostic test

Most of the studies evaluating different EEG modalities have used the sensitivity and specificity, or diagnostic yield, also called positive predictive value (PPV). PPV is defined as the proportion of people with positive test results who have the disease (45). The predictive value is determined by the test's sensitivity and specificity and the prevalence of the disease. The dependence on the prevalence of the disease means that the test's usefulness for an individual patient changes with the prevalence of the disease in the population being tested (45). For instance, predictive values should not be applied to countries with a different prevalence of a SUS.

On the other hand, sensitivity and specificity are independent of the disease prevalence but affected by the disease severity. In the early stages of the disease, as in FSUS, it is difficult to establish a definitive diagnosis (46). It is, therefore, preferable to use likelihood ratios (LR). The LR is calculated using both sensitivity and specificity and is defined as the ratio between the probability of observing results in a patient with the disease in question and the probability of that result in a patient without the condition (47).

Other methodological problems have included both the reliance on rEEG archived data (which is frequently inaccurate, incomplete, and retrospective) as the source of clinical information of the target population and the scarcity of prospective studies.

To date, there is a shortage of research evaluating the ambulatory EEG in patients with FSUS and, particularly, the use of ambulatory EEG in the seizure recurrence.

2.7 Thesis Contributions

This dissertation makes an important contribution to the Clinical Neurology field, particularly to the diagnosis of patients with new-onset of seizure disorders and epilepsy. The primary purposes of this dissertation were to test the following hypotheses:

1. The ambulatory EEG's discriminative power to detect ED in patients who present with FSUS will be comparable to measures reported in the literature for ambulatory EEG and epilepsy (within the range of 75-80%).

2.The sensitivity, PPV and LR for detecting an ED will be better with ambulatory EEG in patients presenting with a FSUS than the first rEEG and second rEEG.

3. The likelihood of seizure recurrence after 52 weeks (one year) of follow-up in a patient who presents with a FSUS will be more than 50%. Also crucial to one-year seizure recurrence will be age, history of brain lesions, stroke and psychiatric comorbidity, presence of nocturnal seizures, and MRI or CT abnormalities.

4.The presence of ED in the ambulatory EEG will be a predictor of seizure recurrence within a year's follow-up.

It should be noted that it is not possible to prove the correctness or falsehood of these hypotheses formally. Instead, this dissertation was limited to provide high-quality evidence for or against their validity. It does so by crafting a prospective study and using STARD that is the standard for reporting diagnostic accuracy studies. As a new modality of EEG, the ambulatory EEG has been suggested by several authors as a promised alternative to other modalities of routine EEG but without a sufficient quality research complement. The use of Ambulatory EEG offers two main advantages over the routine EEG in the detection of ED’s including prolonged recording and inclusion of a sleep sample during the recording. Furthermore, the inclusion of the follow-up time in patients for a seizure recurrence and their relation to the presence of ED in the Ambulatory EEG supports the use of ambulatory EEG as a predictive tool for seizure recurrence after the FSUS.

CHAPTER 3: THEORETICAL PERSPECTIVES

This chapter will explain three underlying theoretical perspectives that will guide this research. The first is the clinimetrics framework, which provides the intellectual basis for clinical phenomena. According to Alvan R Feinstein, “clinimetrics concerns itself with indexes, rating scales, and other expressions that are used to describe or measure symptoms, physical signs, and other distinctly clinical phenomena in clinical medicine” (48).

The second theoretical perspective involved in this research is the conceptual model developed by the Committee on Diagnostic Error in Health Care that has defined diagnostic error and illustrated the diagnostic process, the environment in which this process occurs, and the outcomes that result from this process (26). This conceptual model overlaps with the clinimetrics framework, providing a unified approach.

The last perspective is the validity theory. The validity theory focuses on the clinical test and how it performs.

3.1 From clinical observations to diagnosis.

3.1.1 Clinimetrics.

In a clinical setting, a diagnosis represents an individual's attribute that separates him/her from others (healthy vs. disease). Furthermore, a specific diagnosis suggests that this individual’s outcome will be different (death, accidents, complications, etc.) from that of others; may indicate that the person might be a candidate for treatment; or that his/her life will change following the treatment (49).

3.1.2 Clinical observation and diagnosis

The diagnostic process is a complex enterprise that involves information gathering and clinical reasoning to determine a patient's health problem (26). This process happens over time and within the context of a health care system which may also affect the diagnostic process.

The diagnostic process happens as follows: first, the patient becomes aware of a medical issue and connects with the health care system. Once the assessment has been organized, and the patient is connected with the assessor, the bedside clinimetrics starts with an iterative procedure of data gathering, information integration and interpretation to determine a working diagnosis and ends by categorizing this diagnosis into a defined clinical entity (49). Taking a clinical history, and interviewing the family, conducting a physical exam, performing diagnostic testing or referring to another specialist are included in the process of data gathering. The information-gathering approach can be used at different times, and diagnostic information can be obtained differently. The continuous data-gathering procedure, incorporation of new information, and interpretation involve hypothesis generation and updating of prior probabilities over time (26). A single working diagnosis might be identified, but clinicians might still be working with several diagnoses, generally referred to as the differential diagnosis. It is most common that clinicians will consider more than one diagnostic hypothesis to explain the patient's symptoms, and he/she will refine this hypothesis as data is acquired in the diagnosis process (26). As a diagnostic method proceeds and the list of potential diagnoses becomes narrowed, diagnostic refinement of the working diagnosis becomes subject to analytic verification, in which the lead diagnosis is verified for its adequacy in clarifying the signs and symptoms, its coherency with the patient's unique circumstances (physiology, risk factors), and whether a particular diagnosis is appropriate. When considering diagnostic testing or treatment options, the diagnostic verification step is crucial, making the

diagnostic method's validity one of the critical steps that must be recognized and taken into account in diagnosis making (49).

3.2 Diagnostic error

Getting the correct diagnosis is a crucial aspect of health care. However, this endeavor is far from perfect. Diagnostic error – inaccurate or delayed diagnosis- affects approximately 5% of U.S. adults who seek outpatient care each year. Furthermore, postmortem examination research has shown that diagnostic errors contribute to 10% of deaths, and diagnostic errors are the most common reason for paid medical malpractice claims (26). The Committee on Diagnostic Error in Health Care 2015 concluded that "*most people will experience at least one diagnostic error in their lifetime,*" calling for several changes, including an improvement in the diagnosis process, making the diagnosis a collaborative effort, including the patient in the diagnosis process, and improving the measurements of disease (26). All these factors are integral to the conceptual model to be used in this research.

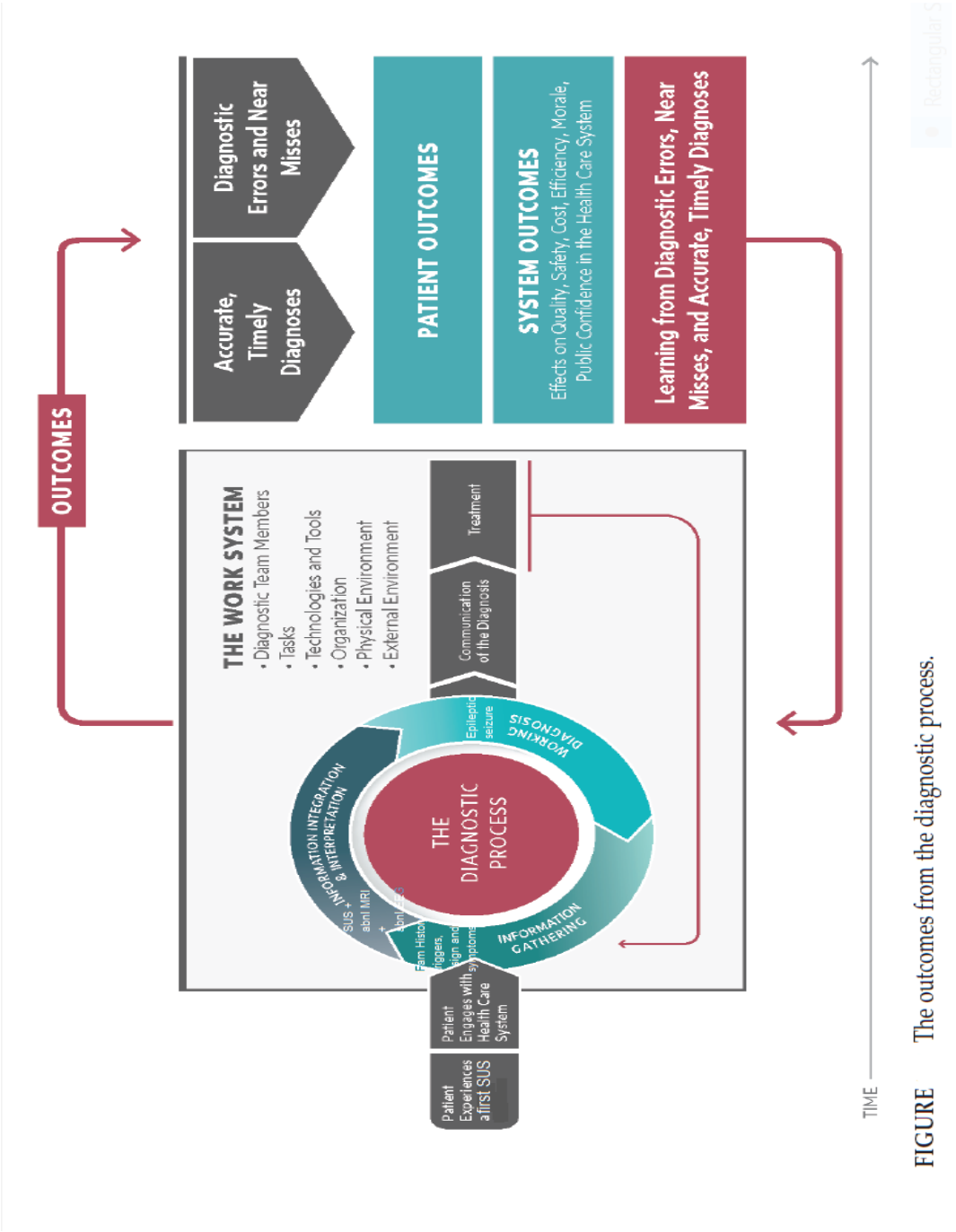


FIGURE The outcomes from the diagnostic process.

Figure 3.1. The figure was taken from the book National Academies of Sciences, Engineering, and Medicine 2015. Improving Diagnosis in Health Care. Washington, DC: The National Academies Press. https://doi.org/10.17226/21794

3.3 Validity theory: Qualitative diagnosis and its validity

Validity refers to “the degree to which evidence and theory support the interpretations of the test results for the proposed uses of the test.” Validity has five essential points (50):

1. Tests are not valid or invalid, but the inferences and applications of the test are more or less valid
2. Validity is an evaluative judgment of the degree to which empirical evidence and theoretical rationales support the adequacy and appropriateness of interpretations and actions based on test scores or other modes of assessment
3. Validity is a unitary concept. Interpretation of the scores must be supported by evidence and/ or theory
4. Each interpretation of a test must be supported logically and empirically.
5. Each use of a test must be supported.

In clinical settings, the term diagnostic test may incorporate at least one clinical observation prompting the diagnosis (such as an epileptic seizure). It may also include a set of findings during the history taking and examination (such as tongue biting and urine incontinence) or any paraclinical procedure (EEG with epileptiform discharge) (49). The degree to which a diagnostic test measures what it is intended to measure is called validity. A diagnostic test's validity has two essential aspects: internal validity and external validity (49).

Internal validity is the diagnostic test's capacity to accurately recognize individuals with the disease and individuals without the condition than reference methods (biopsy, autopsy). The internal validity is assessed with the discriminative power and the clinical predictive value tests such as sensitivity, specificity, PPV, NPV, and LR (49).

On the other hand, external validity is the diagnostic test's capacity to yield comparable results for different populations, different settings, different users, and different conditions. The kappa coefficient is used to measure the external validity (49).

CHAPTER 4: METHODS

4.1 Study design

This study is a prospective cohort study with a one-year (52 weeks) follow-up. A purposive sample of patients was recruited until the required sample size was reached. Patients were contacted a year after the FSUS through the Single Seizure Clinic (SSC).

4.1.1 Study Population

During October 2014 and December 2018, adult patients (>16 years old) referred to the SSC who experienced the first episode of an epileptic seizure and for which a SUS was clinically corroborated were consecutively invited to participate in this prospective study. The epileptologist/neurologist introduced the purpose of the research and implications (i.e., repeat EEG and 24 hrs. ambulatory EEG) of being a participant in this study. After a signed consent, patients were booked for repeat EEG (second rEEG) and ambulatory EEG on the next available date.

4.2.1 Single Seizure Clinic and protocol

The Single Seizure Clinic (SSC) is localized at the Royal University Hospital in Saskatoon, SK, Canada. The SSC started in 2011 and is the only available clinic that provides urgent assessment and evaluation of possible seizure episodes in an ambulatory setting to expedite the epileptologist/neurologist assessment. The SSC accepts referrals from physicians and health providers in the province. The referrals are triaged by a specialized nurse, who books the day and time for the morning first routine EEG (rEEG) and same-day afternoon initial consultation.

4.2.2 Clinical diagnosis and diagnostic evaluation

At the initial consultation, the patient first meets with the SSC nurse, who, after an interview, fills out a standardized assessment form. The nurse presents the case to an

epileptologist/neurologist. Afterwards, the epileptologist/neurologist performs a detailed clinical history of the patient, a detailed description of the seizure and peri-ictal events, and any collateral information, including a history of any previous auras, absences, or myoclonic jerks. Finally, the epileptologist/neurologist performs a neurological examination and reviews previous exams (CT, blood work, etc.) By this time, the results of the patient's first rEEG were accessible to the epileptologist/neurologist. Based on their evaluation, the epileptologist/neurologist confirms that the patient had had an epileptic seizure, provides the diagnosis at the end of the consultation, and initiates treatment with anti-epileptic drugs (ASM) if seizure recurrence is highly likely (i.e., ED on rEEG or ambulatory EEG) or arranges for follow-up without medication as appropriate. For this study's purpose, further investigations were requested (i.e., second rEEG, and ambulatory EEG). A second appointment was scheduled to review the investigations' results if there were any abnormalities.

According to the clinical information, the EEG (routine/ambulatory) and neuroimaging results, classification of generalized, focal, and unknown epilepsy was recorded for each case.

All patients were followed or contacted through the SSC at one year following the FSUS.

4.2.2.1 Electroencephalograms

Upon study enrollment, a second rEEG and ambulatory EEG were arranged.

The ambulatory EEG was recorded using 24 AC channels with four differential and four auxiliary DC channels capable of continuous recording (XLTEK Trex Ambulatory System). EEG 10-mm diameter, gold-plated cup electrodes with a 2-mm center hole were attached to the scalp with collodion, according to the international 10-20 system and secured using a 4x4-8 ply gauze sponge. The patient's head was wrapped with Elastic Retention Netting® to decrease artifact and

ensure electrode placement. An “event” button was attached to the system, permitting an indicator of the patient’s event, which was marked on the EEG recording at the specific time of pressing the event button. Patients were instructed to press the event button for all their events, including any auras or spells. Patients and family members documented events further with a written diary detailing each event's specific time, clinical description, and duration.

The second rEEG was recorded before starting the recording of the ambulatory EEG using the same wrapping. Both standardized routine EEG, first and second, were recorded for 20 min following standard recommendations, including photic stimulation and hyperventilation. For the photic stimulation protocol, the stimulus was applied during closed and opened eyes. The frequency of photic stimulation increased from 2 to 60 Hz. Hyperventilation was achieved by asking the patient to breathe deeply for 3 minutes.

After the setup and second routine EEG recording were finished, the patient was sent home with the ambulatory EEG in place with a diary and instructions to come back the next day (24 hours recording) to end the recording.

Findings were classified into two groups a) Epileptiform records showed generalized spikes and waves discharge, or focal spikes or sharp waves followed by slow waves. b) Records with abnormal slow activity and no associated epileptiform features were coded as abnormal but non-epileptiform. Only records with epileptiform activity (ictal or interictal) during the study period were considered as diagnostic.

4.2.2.2 Standards for accepted care

All the EEGs were performed under the accepted standards for electroencephalography in Canada (51). Specifically, all electrode impedances were equal and not exceeding 5000 Ω (ohms) in routine settings to minimize introducing artifacts into the ambulatory EEG (51,52). Finally, all

readers were licensed neurologists recognized by the Royal College of Physicians and Surgeons of Canada and fully accredited by the Canadian Society of Clinical Neurophysiologists.

4.3 Inclusion and exclusion criteria

Eligible patients were at least 16 years of age, had a suspected single unprovoked seizure, and had been referred to the SSC for assessment. Patients were not eligible if 1) they had more than two events, 2) the initial assessment concluded that the event was not FSUS, 3) they had a previous diagnosis of epilepsy, and 4) if the first seizure was provoked or presented with status epilepticus.

The first single seizure (FSUS) was defined according to the International League against Epilepsy as a “first transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain, in the absence of an identified proximate precipitant factors” (6) or an event of loss of consciousness with signs and symptoms of an epileptic seizure.

All eligible patients were invited to participate in the study and asked for written consent.

4.4 Data collection

4.4.1 Clinical and demographic information

The demographic information was taken from the standardized questionnaire use by the nurse at the SSC. The clinical information, including data of the SUS, the initial assessment, and date of the referral doctor, time of the initial assessment and impression by the epileptologist, results of MRI or CT scans, were gathered after the consent of the patient to participate in the study.

4.4.2 Outcome variables

There were two main outcomes and one secondary outcome. One of the main outcomes was to evaluate the diagnostic test and the other was to determine the risk factors for recurrence

of an unprovoked seizure after FSUS. The association of risk factors with the recurrence of unprovoked seizures was measured in terms of hazard ratios and their 95% confidence intervals.

The first main outcome variable to evaluate the diagnostic test was the clinical diagnosis of epilepsy. The diagnosis of epilepsy is a decision that each neurologist/epileptologist made based on the 2015 ILAE epilepsy definition (14) as follow:

1. At least two unprovoked seizures occurring >24 h apart.

2. One unprovoked seizure with additional features accompanied by circumstances that increase the possibility of a seizure recurrence, such as an epileptiform electroencephalogram (EEG) study or stroke lesion in an imaging study such as Magnetic Resonance Imaging (MRI) or Computed Tomography (CT)).

3. Diagnosis of an epilepsy syndrome such as Dravet's syndrome, childhood absence epilepsy, or juvenile myoclonic epilepsy.

The second main outcome variable to determine risk factors was the recurrence of an unprovoked seizure after FSUS.

Lastly, the secondary outcome was the "time in weeks until an individual presents with a subsequent seizure after the FSUS," and it was evaluated at one year of follow-up through the SSC.

4.4.3 Independent variables for the seizure recurrence

Medical history: a family history (first degree family with epilepsy), history of traumatic brain injury, stroke, and prior neurological surgeries increase the risk of seizure recurrence (53).

Age: Previous studies have shown that elderly patients have a 45% to 62% risk of seizure recurrence one year after diagnosis. Meanwhile, adult patients have a 21% and 45% risk of seizure

recurrence in the first three years following the diagnosis (17). We created two age groups, one including individuals between 17 and 60 years old and the second group with individuals older than 60 years old. This grouping was based on the literature (54–56) and the incidence of epilepsy in Saskatchewan (57).

Sex: Male patients have a higher seizure recurrence than female patients

Presence of nocturnal seizure: the presence of nocturnal seizures increases the risk of seizure recurrence up to 2.5 times compared with patients without nocturnal seizures (3).

Brain lesion: the presence of prior brain lesion or insult on CT or MRI increases the risk of seizure recurrence up to 2.1 times (3).

Developmental disabilities and delay: the presence of any developmental disabilities in an individual has been found to increase the risk for epilepsy. The prevalence of epilepsy in this group is around 30-50% and higher than the general population (58).

Stroke: the presence of cerebral infarction increases the risk of epilepsy up to 17 times higher than the general population (59)

Use of ASM: the use of ASM is associated with risk reduction of seizure occurrence within the next 1-2 years not long-term remission in individuals with single or infrequent seizures (60). In this context is important to remember that the use of ASM was coded as positive if patients confirmed having taken the medication and the medication was not started after seizure recurrence or because of seizure recurrence.

4.5 Sample Size

The sample size was calculated for cohort studies using Epitools epidemiological calculator (https://epitools.ausvet.com.au/?page=home) (61). We expected an incidence of 30%

(62) and assumed a relative risk of two with a confidence level of 95% and power of 80%. The total sample size was 80 patients. However, this number was increased by 15% for the multivariate analysis with the expectation of a RR between 0.5 and 2.0. As a result, a sample size of 94 patients would be adequate.

4.6 Ethical considerations

Ethical approval was obtained from the Biomedical Research Ethics Board at the University of Saskatchewan (#14-30).

4.7 Data

4.7.1 Data collection and data entry

We established a permanent and secure storage system for all the original files, including results of EEGs, SSC notes (copies), and collection tools for each patient following ethics requirements.

The data were entered into the Statistical Package for Social Sciences IBM@ SPSS statistics@ version 27. We used a double-data entry, followed up with a comparison to check for inconsistencies.

4.8 Data analysis

4.8.1 General statistics analysis considerations

Statistical analysis was completed with Statistical Package Social Science (SPSS) Version 27 (SPSS Inc. Armonk, NY: IBM Corp.) and Statistical Analysis System University Edition (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined by an alpha level of 0.05. For each objective, descriptive analysis using frequencies and proportions for categorical variables and median and means with standard deviations and quartiles for continuous variables were completed.

4.8.2 Analysis for Purpose 1 and Purpose 2

The main outcome for purpose1 and 2 was 1) the evaluation of the discriminative power and clinical predictive value of the ambulatory EEG (sensitivity, specificity, PPV, NPV, and LR) for epileptiform activity in patients presenting with a FSUS and 2) the assessment of the discriminative measures of the Ambulatory EEG compared with first and second rEEG. The Standards for Reporting of Diagnostic Accuracy (STARD) statements and guidelines were followed (63).

The first step in calculating sensitivity, specificity, PPV and NPV was to make a 2 X 2 table with patients allocated to groups according to the presence or absence of the outcome (clinical diagnosis of epilepsy) in columns and categories to test (first rEEG, second rEEG, and ambulatory EEG) in rows.

Sensitivity (%) was defined as the proportion of subjects with the outcome who had a positive result.

Specificity (%) was defined as the proportion of subjects without the outcome who had negative results.

Positive Predictive Value (%) was defined as the proportion of subjects with a positive test result that had the outcome.

Negative Predictive Value (%) was defined as the proportion of subjects with a negative test result who did not have the outcome (45).

A corroborating nonparametric Area Under the Curve (AUC) analysis was also performed to compare the tests' results in the entire study cohort (64).

The likelihood ratio for a positive test (LR+) was defined as the probability of a subject with the outcome (clinical diagnosis of epilepsy) having a positive test divided by the probability of an individual without the outcome of having a positive test.

$$\frac{Probability\ of\ a\ subject\ with\ the\ outcome\ having\ a\ positive\ test}{Probability\ of\ a\ subject\ without\ the\ outcome\ having\ a\ positive\ test}$$

A LR+ greater than one meant that the positive test was more likely to occur in patients with the outcome of clinical diagnosis of epilepsy. LR+ less than one indicated that a positive test was less likely to occur in patients with the outcome than the patients without the outcome(47).

The likelihood ratio for a negative test (LR-) was defined as the probability of a subject with the outcome of having a negative test divided by the probability of an individual without the outcome of having a negative test.

$$\frac{Probability\ of\ a\ subject\ with\ the\ outcome\ having\ a\ negative\ test}{Probability\ of\ a\ subject\ without\ the\ outcome\ having\ a\ negative\ test}$$

LR- greater than one meant that a negative test was more likely to occur in patients with the outcome than in patients without the outcome. LR- less than one meant that a negative test is less likely to occur in patients without the outcome (47).

The Receiver Operating Characteristic (ROC) curves were constructed by plotting each test's sensitivity and specificity pair on a graph with the 1-specificity on the x-axis and sensitivity of the y-axis. The area under the curve (AUC) aimed to estimate the discriminative power of a test. The closer the curve followed the upper left-hand corner and the larger the area under the curve, the better the test was at discriminating between those with and without the outcome(64).

The AUC has been used to assess discriminatory ability statistical methods, mathematical models, and diagnostic tests (64). Especially, Swets (65) showed that using the results of a signal detection experiment employing the two-alternative forced-choice (present/absent), the AUC

corresponds to the probability of correctly identifying which of the two stimuli is “noise” and which is “signal plus noise.” When an investigator calculates AUC directly from a rating experiment, mathematically, he/she is reconstructing random pairs of images, one from a diseased individual and one from the normal individual, and using the reader’s separate rating of these two images to stimulate what the reader would have decided if these two images had in fact been presented together as a pair (64). More important, it has been recognized by Bamber (66) that this “probability of correctly ranking a (normal, abnormal) pair is hyperconnected with the quantity calculated in the Wilcoxon or Mann Whitney-U statistical test.

Consequently, AUC and ROC curves are used to compare different imaging techniques, which have the advantage of combining graphic methods for obtaining a smoothed areas and a computational formula for its standard errors (67).

4.8.3 Analysis for Purposes 3 and 4

The main outcome for Purpose 3 and 4 was 1) to identify risk factors associated with seizure recurrence and 2) assess if the presence of epileptiform activity on the ambulatory EEG was associated with increased risk of seizure recurrence in patients who present with a FSUS after one year of follow-up (52 weeks).

After 52 weeks (one year) of follow-up, descriptive and bivariate analyses were performed for the outcome (seizure recurrence) and each independent variable. We analyzed the data as a “first recurrent not competitive ” event (68).

The cumulative risks of recurrence were determined by life-tables methods, with an event defined as the first unprovoked seizure recurrence. These methods consider the length of follow-

up in each individual. Therefore, the computed risk represents the risk of recurrence conditional on surviving seizure-free through the specified time (follow-up) interval.

Univariable analysis (Kaplan-Meier survival curves) was used for each variable relates to the cumulative percent recurrence to the time after FSUS.

For this dataset, it was assumed that all survival times were independent of each other; censoring occurred randomly and solely as right-censoring and, it was non-informative (69).

The start time within the analysis was considered as the day (specific date) of the FSUS. The survival time was measured by weeks. The event was considered the “time in weeks until an individual presents with a seizure recurrence” The seizure recurrence was regarded as recurrence of unprovoked seizures during one-year follow-up. Censoring occurred for three reasons (68):

1) the individual did not have any seizure recurrence during the study period

2) the individual was lost to follow-up during the study period

3) the individual was withdrawn from the study because of death or some other reason.

The Cox Proportional Hazard (PH) model was used to estimate univariable and multivariable ratios for the association of ED on the Ambulatory EEG and other variables with the seizure recurrence in patients with FSUS. Strengths of association were assessed by hazard ratios (HR) and with 95% confidence interval (95%CI) and were considered significant when the 95% confidence interval's bounds did not include unity.

The modelling followed the next steps:

Step 0: Descriptive statistics. Percentage, totals, medians with dispersion analysis was be used to characterize the population under study.

Step 1: The Kaplan Meier method was used to calculate unadjusted survival probability. The log-rank test was used to compare survival curves. A univariable non-parametric survival model was used to identify predictors for the multivariable model based on a p-value ≤ 0.25.

Step 2: A multivariable Cox PH model was used for the adjusted analysis. A (full) model used for prediction purposes contained all predictors significant at p-value= ≤ 0.05 and any other variable of clinical importance. Then, a backward model selection method was used to eliminate any covariates that were not statistically significant (p-value= >0.05).

Step 3: The PH assumption of the Cox PH model was examined by two methods: a) examining the significance of the interactive effect between time and covariates in the model and b) examining covariate-wise residuals (Schoenfeld residuals) (70). Schoenfeld residuals are one of the goodness of fit testing approaches for assessing the PH assumption. The residuals are defined for each predictor in the model and for every subject who has the event. The residuals are the observed value of the variable under study minus the weighted average of the same variable in the population under investigation still at risk at time *t*. The weights are each subject's hazard. The idea behind the statistical test is that if the PH assumption holds for a particular covariate, then the Schoenfeld residuals for that covariate will not be related to survival time (71).

Step 4: The final model with significant interactions and confounders was obtained.

Confounders were investigated by measuring change between unadjusted and adjusted β values. To determine whether the confounding was present, we deemed significant a difference >20% change in β's values. Interactions were investigated by measuring their statistical significance. To determine if the interaction was present, we deemed them significant if the p-value was <0.05 (72).

CHAPTER 5: RESULTS

5.1 Population

Among the 125 individuals invited to participate in the study from October 2014 through December 2018, 122 consented to participate. Of the 122 participants, 22 were eliminated due to exclusion criteria. Most excluded patients had syncope or provoked seizures as the first clinical diagnosis (fig 5.2). Thus, the study population comprised 100 patients with a clinical diagnosis of first unprovoked seizure, aged 17-82 years (mean 41.8, median 36.5) for whom a complete follow-up of 52 weeks after FSUS was obtained (see Table 5.1).

Of the 100 patients in the cohort, 58% were females, and 21% of these individuals were older than 60 years old.

Also, 63% of the patients were referred to the SSC by the ER physician, 35% by a family physician, and 4% by other physicians (see Table 5.1).

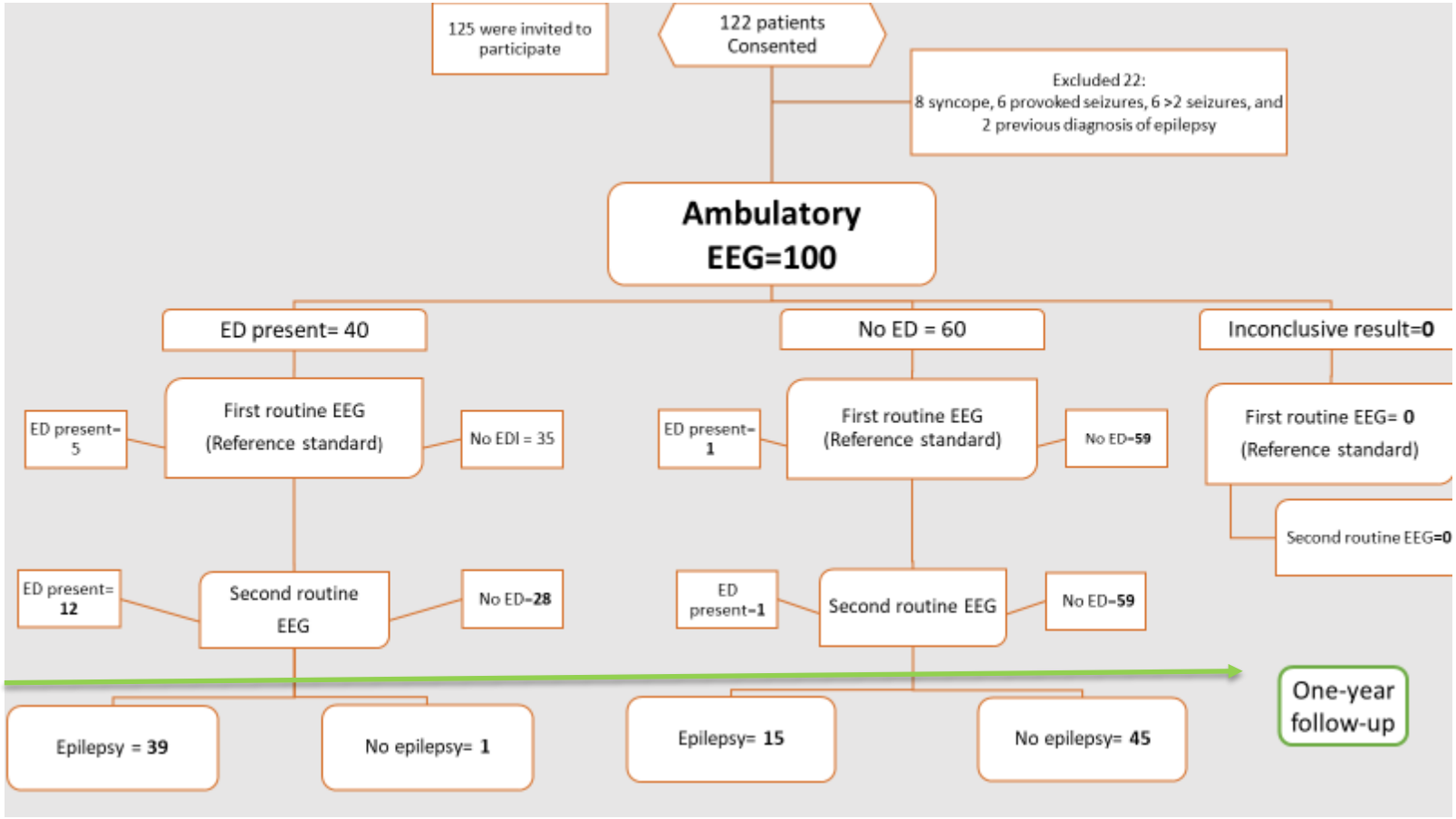


Figure 5.2. Flow diagram for study diagnostic performance of the ambulatory EEG versus routine EEG and risk factors for seizure recurrence among individuals with first single unprovoked seizures.

ED= epileptic discharges sharp or spike waves.

Table 5.1 Cox unadjusted baseline characteristics of the study individuals (n=100)

Characteristic	Epilepsy=54 No. (%)	No Epilepsy = 46 No. (%)	Total=100 No.	Hazard Ratio (95%CI)	*p*-value
Age in years at FSUS					
Mean	44.5	38.6	41.8	0.98(0.96, 1.00)	0.18
Median	45.4	53.0	36.5		
(Quartile 25-75)			(27 - 59)		
Age group:					
17-59(reference)	38(48%)	41(52%)	79		
≥60	16 (76%)	5(24%)	21	0.74(0.3,1.8)	0.72
Sex:					
Male	21(50%)	21(50%)	42	1(0.51,2)	0.96
Female (ref.)**£**	33(57%)	25(43%)	58		
History of:					
A FM***** with epilepsy	11(65%)	6(35%)	17	1.8 (0.8,4)	0.15
Febrile seizures	1 (25%)	3(75%)	4	0.05(0,38.4)	0.37
Developmental delay	0	3(100%)	3	0.05(0,107)	0.44
Psychiatric comorbidity	10(34.5%)	19(65.5%)	29	1.6(0.7,3.7)	0.27
Head trauma	8(42%)	11(58%)	19	0.74(0.3,1.9)	0.53
Brain surgery	3(75%)	1(25%)	4	1.7 (0.4,7.2)	0.46
Brain tumour	3(75%)	1(25%)	4	1.9(0.5,8)	0.36
Stroke	2(100%)	0	2	5.6(1.3,24.2)	0.02
Systemic Hypertension	7(70%)	3(30%)	10	0.9(0.3,2.8)	0.80
Tongue biting	16(55%)	13(45%)	29	1.2(0.57,2.5)	0.67
Incontinence	9(69%)	4(31%)	13	0.62(0.2,2)	0.44
Confusion	33(52%)	31(48%)	64	1(0.5,2)	0.90
Automatism	3(43%)	4(57%)	7	1.3(0.4,4.2)	0.68
Nocturnal seizures	15(79%)	4(21%)	19	1.37(0.6,3)	0.44
ASM taken	44(100%)	0	44	0.02(0.003,0.2)	<0.001
CT/MRI (abnormal)	15(68%)	7(32%)	22	0.94(0.4,2)	0.90
Ambulatory EEG (ED presence)	39(97.5%)	1(2.5%)	40	2.9(1.5,5.9)	<0.001
Referral physician:					
Emergency room			61 (63%)		
Family			35 (35%)		
Others			4 (4%)		

* FM: Family member
£Ref: reference variable

5.2 Clinical diagnosis and follow-up

The overall diagnosis of epilepsy based on the ILAE definition of epilepsy (14) was 54% (54 cases), although seizure recurrence was present only in 33 individuals. The final diagnoses for the patients in the cohort are listed in Table 5.2. A total of six individuals had incomplete follow-up because the patient chose to terminate our follow-up contact.

The diagnosis of epilepsy (based on clinical characteristics, first rEEG, and imaging before the ambulatory EEG) was made on thirteen patients. In only five cases was the ascertainment of ED consistent between the first rEEG and the ambulatory EEG.

Among the 54 cases with a diagnosis of epilepsy, seizures were categorized as focal in 31 individuals (57%), generalized seizures in 11 individuals (20.4%), unknown in 11 individuals (20.4%), and combined generalized and focal seizure in 1 individual (2%). The clinical diagnosis was based on clinical information, EEG, and imaging results.

Among the 54 patients with a diagnosis of epilepsy, factors that may have increased the risk before the first unprovoked included: one individual with febrile seizures, eight individuals with head trauma (unconsciousness or amnesia lasting longer than 30 minutes, skull fractures, or intracranial bleeding), three individuals with a history of brain surgery, two individuals with cerebrovascular disease (stroke), seven with hypertension, three with history of brain tumor and three with history of brain surgery. We did not find individuals with a history of neonatal seizures, central nervous-systemic infection, asphyxia at birth, central nervous system abnormalities, or any developmental disability. In addition, there were ten individuals with psychiatric comorbidity and three individuals with mild developmental delay (see Table 5.1).

Table 5.2 Final diagnosis† among cohort individual with FSUS (n=100)

Diagnosis	No. (%)
Epilepsy	54(54%)
Focal	31(57%) ‡
Generalized	11(20.4%) ‡
Unknown	11(20.4%) ‡
Combined (generalized and focal)	1(2%) ‡
Single unprovoked seizure	38 (38%)
Syncope	7(7%)
Psychogenic non-epileptic seizures	1(1%)

†Final diagnosis after clinical assessment +imaging +EEG
‡ Percentage among patients with epilepsy

The treating epileptologist/neurologist recommended initiation of ASM in 52 individuals (52/54) at their FSUS time, but only 45 individuals took the medication. The main reason for not taking the ASM among these individuals was personal (such as the use of marijuana, wanting to be pregnant, etc.). Among the ten individuals who were not taking ASM, nine had a seizure recurrence and of the 33 individuals who presented with seizure recurrence, 15 were already taking ASM.

Lamotrigine was prescribed on 30 patients (57%), phenytoin on 13 patients (24.5%), clobazam in five patients (9.4%), levetiracetam in four patients (7.5%), and topiramate in one patient (2%).

5.3 Wait times and time intervals

The mean wait time for the first assessment after FSUS by an epileptologist/neurologist at the SSC, including the first rEEG, was 9.9 weeks. Meanwhile, the time interval between the FSUS

and the ambulatory EEG was 12 weeks, and the time between the first routine EEG and ambulatory EEG was 1.6 weeks (see table 5.3).

Table 5.3 Wait-times and time intervals for the cohort (n=100)

Time between	Mean in weeks (SD)
FSUS and 1st consult SSC	9.94 (± 7.2)
FSUS and 1st rEEG	9.94 (± 7.2)
FSUS and 2nd rEEG	12 (± 1.6)
FSUS and Ambulatory EEG	12 (± 1.6)
1st rEEG and ambulatory EEG	1.6 (±3.7)

FSUS= first single unprovoked seizure, rEEG=routine EEG

5.4 Electroencephalograms analysis

5.4.1 Discriminative Power of Ambulatory EEG

A total of 100 individuals underwent the first rEGG, second rEEG and ambulatory EEG. There were no missing data or inconclusive results.

The ability of the ambulatory EEG to identify individuals with the diagnosis of epilepsy (sensitivity) was 72%, compared with 11% of the first rEEG (*p*-value:< 0.001) and 22% of the second rEEG.

The ambulatory EEG's ability to identify individuals without epilepsy (specificity) was not significantly different from the first rEEG nor the second rEEG (98% vs. 100% and 98%, respectively).

With a prevalence of 54%, the ambulatory EEG's predictive ability to identify patients with a diagnosis of epilepsy (PPV) was 97% compared with 100% for the first and 92% for the second rEEG. On the other hand, the ability of the ambulatory EEG to identify patients without

epilepsy in individuals without ED findings (NPV) was 75% compared with 49% for the first rEEG and 52% for the second rEEG (see Table 5.4).

In general, the global diagnostic accuracy of ambulatory EEG for detecting individuals with a diagnosis of epilepsy revealed an Area Under the Curve (AUC) of 0.85 (95%CI: 0.77, 0.93) for ambulatory EEG compared with 0.56 (95%CI: 0.44,0.67) for the first rEEG and 0.60 (95% CI: 0.49,0.71) for the second rEEG. (Table 5.5 and Figure 5.3).

Table 5.4 Diagnostic Accuracy of different modalities of EEG for all patient with First Single Unprovoked Seizure with a clinical diagnosis of epilepsy (n=100)

	First Routine EEG		Second Routine EEG		Ambulatory EEG	
	Epilepsy diagnosis		Epilepsy diagnosis		Epilepsy diagnosis	
Variable	Positive	Negative	Positive	Negative	Positive	Negative
No. Abnormal test	6	0	12	1	39	1
No. Normal test	48	46	42	45	15	45
Total no. test	54	46	54	46	54	46
Sensitivity (95% CI)	11 (4.5,23)		22(12,36)		72(58,83)	
Specificity(95%CI)	100 (89,100)		98(87,99.8)		98(87,100)	
PPV (95%CI)	100(52,100)		92(62,99.6)		97(85,100)	
NPV (95%CI)	49 (38,59)		52 (41,63)		75(62,85)	
LR (Positive [C]))	Infinity		10(1.4,77.3)		33(4.7,232.5)	
LR (Negative [C])	0.88(0.80,0.97)		0.8(0.7,0.9)		0.28(0.18,0.44)	
LR (Positive [W])	Infinity		12(1.8,79)		39 (5.6,270)	
LR(Negative[W])	1(0.83,1.3)		0.91(0.71,1.2)		0.33(0.21,0.52)	

Prevalence 54%, PPV=positive predictive value; NPV=negative predictive value, LR w/prevalence=Likelihood ratio [C]=conventional, [W]=weighted by prevalence

Table 5.5 Area Under the Curve (AUC) for the three competitive EEGs modalities among 100 individuals with FSUS to identify epileptiform discharges with a clinical diagnosis of epilepsy

EEG modality	AUC (95% CI) †	Asymptotic significance‡
First routine EEG	0.56 (0.44,0.67)	0.34
Second routine EEG	0.60 (0.49,0.71)	0.08
Ambulatory EEG	0.85(0.77,0.93)	<0.001

†Small 95%CI means that the model requires less input to provide a recommendation

‡ An asymptotic significance less than 0.05 is better than guessing

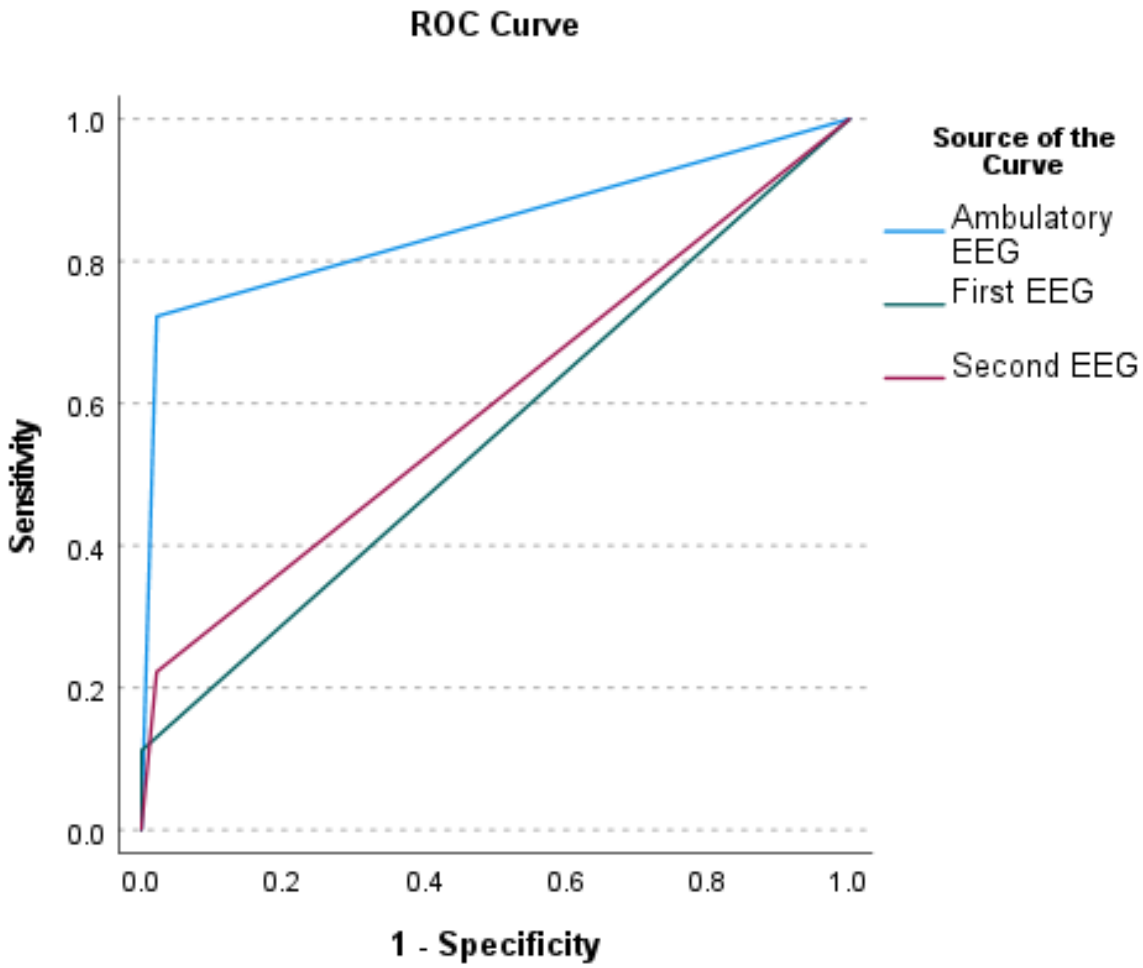


Figure 5.3 Receiver Operating Curves (ROC) based on three EEG modalities for 100 individuals with FSUS to identify epileptic discharges with a clinical diagnosis of epilepsy.

5.4.2 Clinical predictive value of Ambulatory EEG

The ambulatory EEG was 39 times more likely to show epileptiform discharge in individuals with a clinical diagnosis of epilepsy than in individuals without epilepsy (wLR+). On the other hand, the ambulatory EEG was 0.33 (67%) less likely to show an absence of epileptiform discharge in an individual with an epilepsy diagnosis than one without epilepsy (wLR-). (Table 5.4).

5.5 Seizure recurrence and associated risk factors- One-year outcome

5.5.1 Overal risk of seizure recurrence-Life-table estimates

Based on the lifetables results (Table 5.6) among individuals with FSUS, the seizure recurrence was estimated to be 21%, 30%, and 36% at 12, 24 and 52 weeks, respectively, following the first SUS. The estimated hazard function graph (Figure 5.5) shows that the recurrence rate increased to its highest in the 8th week after the FSUS (0.030). The recurrence rate decreases from the end of the 8th week to the 22nd second week (0.004). After the 22nd week, there is an increase of recurrence (0.014), no higher than the initial rate, after which the recurrence rate decreases again (0.001) and remains relatively constant until the end of the follow-up (see Figure 5.4).

Table5.6 Life table of a cohort of individuals with FSUS (n=100)

Interval in weeks of F/U ***ti*†**		Number of seizure recurrence cases *ti*	Number of individuals without recurrence before ***ti***	Probabilities of remaining free of seizures at different ***ti*‡**	Probabilities of seizure recurrence at different ***ti*** (Failure Function) **£**
Lower	Upper				
0	4	5	0	1.00	0
4	8	10	4	0.95	0.05
8	12	5	4	0.84	0.15
12	16	5	4	0.79	0.21
16	20	2	2	0.74	0.26
20	24	1	1	0.71	0.29
24	28	3	2	0.70	0.30
28	32	2	0	0.66	0.34
32	36	0	1	0.64	0.36
36	40	0	0	0.64	0.36
40	44	0	2	0.64	0.36
44	48	0	1	0.64	0.36
48	52	0	0	0.64	0.36
52	.	0	46	0.64	0.36

†*ti*: Time of follow-up on weeks.

‡Survival function: *Si* is the unconditional probability of remaining free from further seizures. $Si = P(T > ti) = \pi\left(1 - \frac{cases\ at\ ti}{remaining\ individuals\ at\ ti}\right)$

£ Failure function F(t) unconditional probability that a randomly selected individual from the population will have a seizure. $F(t) = \Pr(T \leq t), t \geq 0 = (1 - Si)$

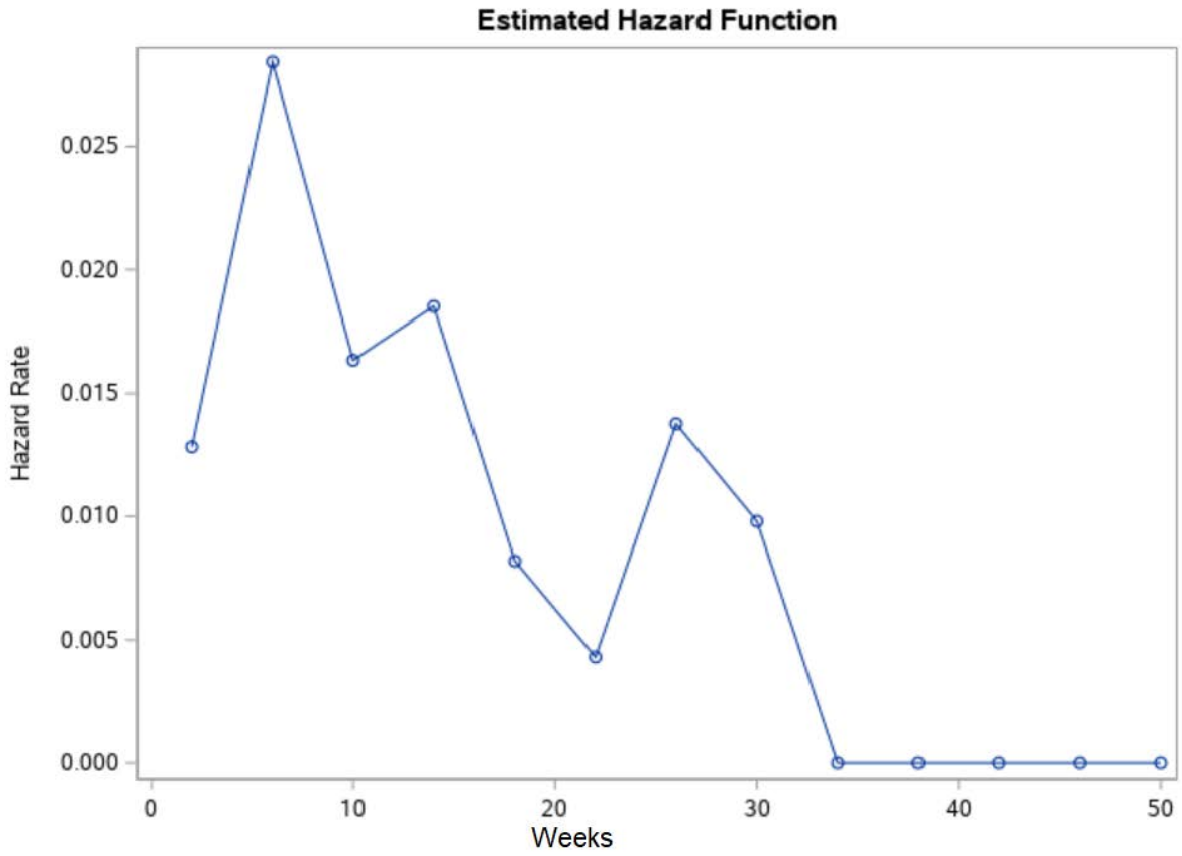


Figure 4.5 Lifetable estimate of failure function for a cohort of patients with FSUS (n=100)

Failure function F(t) is the unconditional probability that a randomly selected individual from the population will have further seizures. $F(t) = \Pr(T \leq t), t \geq 0 = (1 - Si) \times 100$

5.5.2 Impact of risk factors and the presence of ED in the ambulatory EEG on seizure recurrence

Among patients with FSUS, the presence of febrile seizures, psychiatric comorbidity, presence of nocturnal seizures, history of stroke, age group >60 years, use of ASM, and epileptiform activity on the ambulatory EEG were independently associated with a higher risk of seizure recurrence at 52 weeks in the bivariable analysis (see Table 5.7).

Table 5.7 Bivariate analysis as estimated by log-rank and Cox regression of characteristics for demography and risk factors for seizure recurrence in the cohort of patients with First Single Unprovoked Seizure evaluated for the initial model† (n=100)

Risk Factors	Reference category	Log rank‡	HR (95%CI) †	*p-value*
Age	17-60	0.49	0.74(0.3,1.8)	0.21[M]
History of:				
Family member with epilepsy	No	0.15	1.79 (0.80,3.99)	0.15
Febrile seizures	No	0.17	0.05 (0.0,38.3)	0.37
Developmental delay	No	0.24	0.05(0.0,107.4	0.44
Head trauma	No	0.53	0.74 (0.3,1.9)	0.53
Psychiatric comorbidity	No	0.26	0.62(0.27,1.43)	0.26
Stroke	No	0.00	5.69(1.33,24.39)	0.01
Systemic hypertension	No	0.80	0.86 (0.3,2.8)	0.80
Tongue biting	No	0.66	1.2 (0.6,2.4)	0.67
Incontinence	No	0.43	0.6(0.2,2)	0.44
Confusion after event	No	0.95	0.98 (0.5,2)	0.90
Automatism/behavioral	No	0.68	1.3 (0.39, 4.2)	0.68
Nocturnal seizures	No	0.44	1.36 (.61,3.0)	0.43
Antiepileptic drug initiation	No	<0.001	12.78(6.03,27.09)	<0.001
CT/MRI	Normal	0.88	0.91(0.4,2)	0.90
Ambulatory EEG	Absence of ED	0.002	2.97 (1.47, 6.00)	0.00

† Bivariate hazard ratios (HR) estimated by Cox PH regression analysis for seizure recurrence at 52 weeks
‡p-value based on the Log rank
£ Epileptiform discharge

Factors significant at ≤ 0.25 as well as factors with known clinically significance were entered into the initial Cox Proportional Hazard Ratio model and tested for interaction, confounding, and PH assumptions. We found that older age group was a confounder in the association between ED in the ambulatory and seizure recurrence. However, the association between ED in the ambulatory EEG and seizure recurrence at 52 weeks remained significant when it was adjusted by age group. Older age was statistically positively correlated with the presence of ED in the ambulatory EEG but negatively correlated with the seizure recurrence. The effect is

shown in Table 5.8, Figure 5.6, and Figure 5.8, where unadjusted and adjusted β's changed, and the explanatory model is described.

We also found that the use of ASM was a confounder in the association between seizure recurrence and the presence of ED in the ambulatory EEG. However, the association between ED in the ambulatory EEG and seizure recurrence at 52 weeks remained statistically significant when was adjusted by the use of ASM. The use of ASM was statistically positively correlated with the presence of ED in the ambulatory EEG and statistically positively correlated with the seizure recurrence.

These results from the final model show that at any point after FSUS and adjusted by age group and use of ASM, seizure recurrence occurred at 3.2 times (32%) higher rate in individuals with the presence of epileptiform discharge on the ambulatory EEG than individuals without ED on the ambulatory EEG.

Similarly, at any point after FSUS and adjusted by age group and presence of ED in ambulatory EEG, the seizure recurrence occurred at a 12.8 times higher rate in individuals using ASM than individuals not using ASM.

On the other hand, we found that at any point after a FSUS and adjusted by presence of ED on the ambulatory and the use of ASM, seizure recurrence in patients older than 60 years old dropped 73% compared with the younger (17-60) group (see Table 5.10).

Table 5.8 Unadjusted and adjusted Cox PH regression examining the association between ED in the ambulatory EEG and seizure recurrence adjusted by >60 years old age in 100 patients with FSUS

A) Unadjusted

	Seizure Recurrence Crude model		
	$\beta_{unadjusted}$	$HR_{unadjusted}$	*p-value*
ED in the ambulatory EEG	1.090[a]	2.98[a]	0.002

HR, Hazard Ratio
Unadjusted Model
[a.] $h\big(tX(t)\big) = h_0(t)\exp[\beta_1 \boldsymbol{AMB}]$

B) Adjusted

	Seizure Recurrence Adjusted model		
	$\beta_{adjusted}$	$HR_{adjusted}$	*p-value*
ED in the ambulatory EEG	1.38[b]	3.99[b]	<0.001
Patients >60 years of age [b]	-0.93 [b]	0.39 [b]	0.0502

HR, Hazard Ratio
Adjusted Model
[b.] $h\big(tX(t)\big) = h_0(t)\exp\left[\beta_1 \boldsymbol{AMB} + \beta_2 \boldsymbol{Agegroups2}\right]$

Table 5.9 Unadjusted and adjusted Cox PH regression examining the association between Epileptic Discharge in the ambulatory EEG and seizure recurrence adjusted by use of antiseizure medication in 100 patients with FSUS

A) Unadjusted

	Seizure Recurrence Crude model		
	$\beta_{unadjusted}$	$HR_{unadjusted}$	*p-value*
ED in the ambulatory EEG	1.090[a]	2.98[a]	0.002

HR, Hazard Ratio
Unadjusted Model

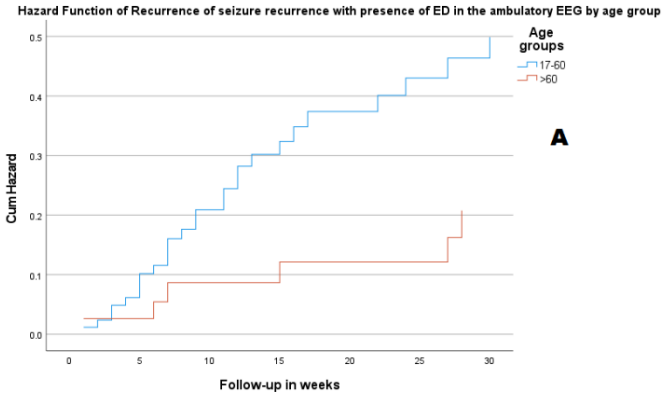
[a.] $h\big(tX(t)\big) = h_0(t)\exp[\beta_1 \boldsymbol{AMB}]$

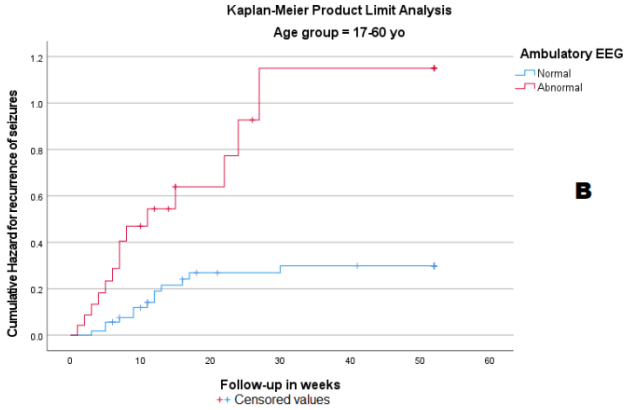
B) Adjusted

	Seizure Recurrence Adjusted model		
	$\beta_{adjusted}$	$HR_{adjusted}$	*p-value*
ED in the ambulatory EEG	0.69[b]	2.0[b]	0.06
Use of ASM [b]	2.33 [b]	10.28 [b]	<0.001

HR, Hazard Ratio
Adjusted Model

[b.] $h\big(tX(t)\big) = h_0(t)\exp\left[\beta_1 \boldsymbol{AMB} + \beta_2 \boldsymbol{AED}\right]$





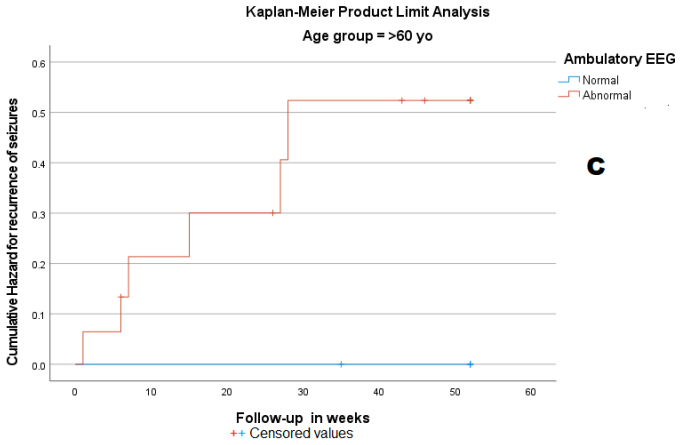


Figure 5.5 A- Hazard function plot of the association between seizure recurrence and presence of epileptiform discharge in the ambulatory EEG stratified by age group among patients with FSUS (n=100)

B-C Kaplan-Meier plots assessing the association between seizure recurrence and the presence of epileptiform discharge in the Ambulatory EEG stratified by age group among patients with FSUS (n=100)

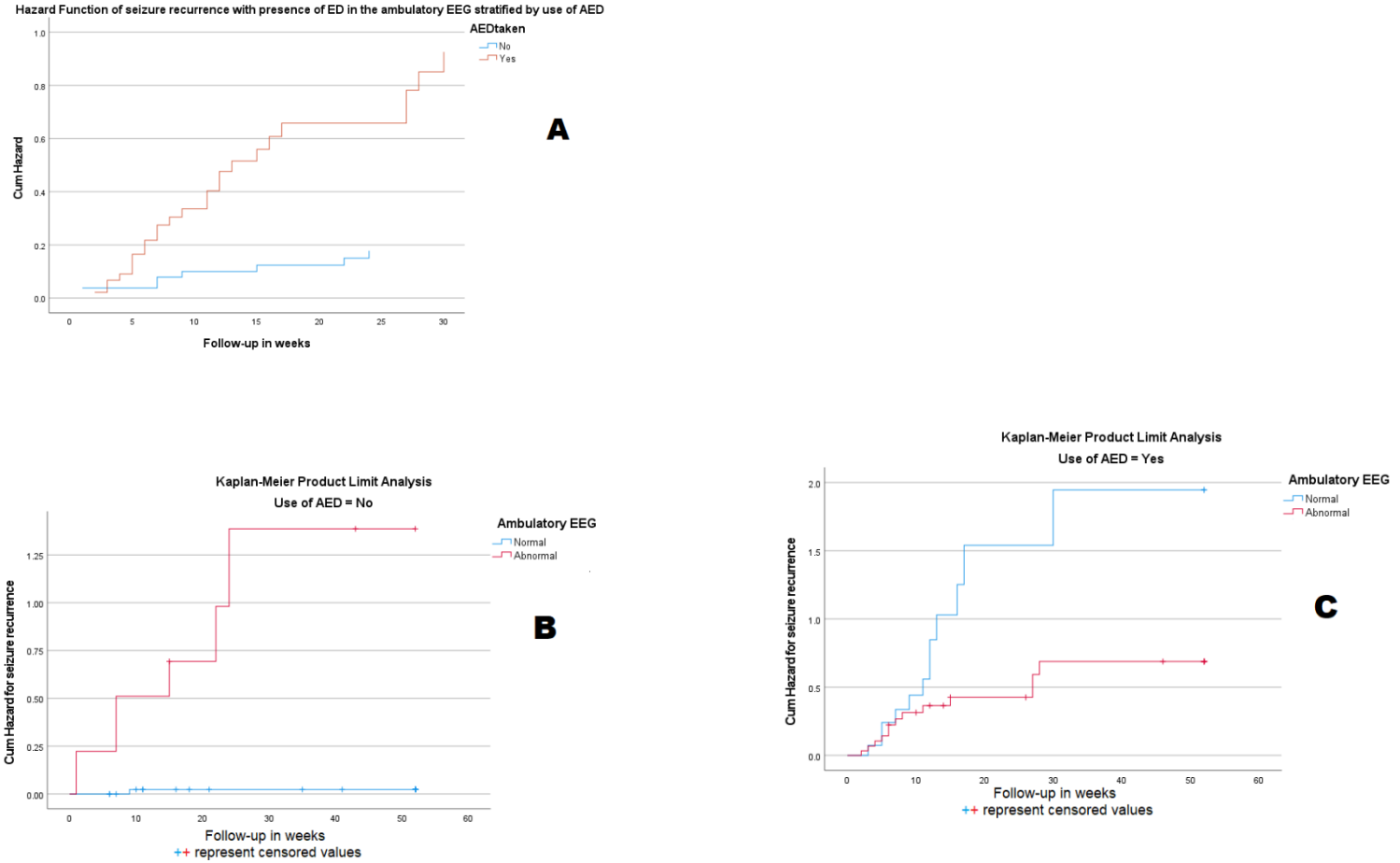


Figure 5.6 **A- Hazard function plot of the association between seizure recurrence and presence of epileptiform discharge in the ambulatory EEG stratified by use of ASM among patients with FSUS (n=100)**

B-C- Kaplan-Meier plots assessing the association between seizure recurrence and the presence of epileptiform discharge in the Ambulatory EEG stratified by use of ASM among patients with FSUS (n=100)

Table 5.10 Final Cox Proportional Hazard model for risk factors of seizure recurrence in a cohort of individuals with FSUS (n=100)

Risk Factors	Category	HR (95%CI)	*p*-value
Age	>60	0.27(0.10,0.74)	0.010
Use of ASM	Yes	12.85(5.64, 29.27)	<0.001
Ambulatory EEG	Presence of ED	3.17(1.47, 6.83)	0.003

No. of subjects=100. Log likelihood=216.597
HR: Hazard ratios, CI= Confidence interval

CHAPTER 6: DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

6.1 Discussion

This research sought to advance knowledge in the field of diagnostic testing among individuals who present with FSUS by assessing the discriminative power and clinical predictive value of the use of ambulatory EEG for the detection of epileptiform discharge compared with the first and second rEEG. We also aimed to find the association between the presence of ED on the ambulatory EEG as a better strategy to forecast the seizure recurrence.

As described in Chapter 2, routine EEG remains central in the diagnosis of epilepsy (further seizure recurrence) as the last definition of epilepsy by the ILAE includes the presence of a single unprovoked seizure plus the presence of epileptiform discharges in the routine EEG (32). However, as a diagnostic test, the rEEG has limited sensitivity (up to 17%) and depends on when and how frequently it is administered.

Although numerous studies have examined several methods aiming to predict the seizure recurrence in individuals with FSUS, few gains have been made to improve these efforts. Consequently, little has occurred to advance our knowledge in this field (73).

An alternative method presented here is the use of Ambulatory EEG. This method offers excellent convenience, low cost, improved access, greater sampling of natural sleep and circadian rhythms, and better diagnostic yield for identification, classification and localization of seizures in patients with an already established diagnosis of epilepsy (74).

6.1.1 Discriminative power and clinical predictive value of the Ambulatory EEG

In the present study, we found that the ambulatory EEG had a significantly better sensitivity, improved NPV and, as a whole, was a better diagnostic test to detect ED than the first and second rEEG among individuals who presented with FSUS.

Our results are understandable in light of the technical advantages of ambulatory EEG over routine EEGs. With the ambulatory EEG, a greater sampling of natural sleep and circadian rhythms and longer recording time are advantages. Furthermore, most ambulatory EEG systems are light and easy to use (52).

On the other hand, historically, a serious problem with ambulatory EEG has been the presence of artifacts. Artifacts are present in all EEG recording modalities and are increasingly more likely as the span of the recording increments increases (52). However, novel techniques are evolving to avoid the most common types of artifacts during the ambulatory EEG's recoding (52). Furthermore, the use of minimal standards to complete the electroencephalograms, such as minimal impedance limits of 5000 Ω, may decrease the frequency of artifacts. In this study, none of the completed electroencephalograms (routine and ambulatory) were inconclusive.

Despite best efforts, one of the weaknesses of this study was the lack of reliability measures. Research has shown that inter-rater (agreement among raters) and intra-rater (individual agreement) reliability are generally low for EEG's interpretation. Furthermore, kappa for intra-rater reliability is better (range from 0.33 to 0.73) than inter-rater kappa (range of 0.29 to 0.62) of the EEG interpretation (75). Also, high confidence in interpretations among readers had low to moderate inter and interrater reliabilities. On the other hand, knowledge of the patient's history, which includes the indication for EEG, patient's age, description of the seizure, results of imaging

test, and technologist comments, increases both reliabilities. In this study, each reader knew the patient's history and performed the clinical assessment, making it difficult to make objective reliability measures. Moreover, the set of three EEG's (first, second, and ambulatory) was interpreted by the same reader. As a whole, this situation simulates the reality of most of the neurology clinics around the world.

Predicting seizure recurrence does not mean better management or prevention of further seizures, as it has shown in previous studies (3). Instead, this study aimed to decrease diagnostic errors, defined as " the failure to establish accurately and in a timely fashion the health status of the individual and communicate effectively this to the patient" (26). The evidence supporting this view is given in Table 5.5. The number of ED detected by the ambulatory EEG and missed by the first and second routine EEGs was significant. These are precisely the individuals that may have adverse outcomes such as recurrence of multiple seizures or even death.

6.1.2 Seizure recurrence after FSUS

Several studies on the risk of seizure recurrence after FSUS, including two randomized clinical trials, have shown that among untreated individuals with ASM, 40-50% can expect a recurrence within two years of the index seizure (73).

The seizure recurrence in this study was 36% at 52 weeks (one year) of follow-up. The frequency of seizure recurrence is consistent with previous studies with similar populations (76,77). Known predictors for the first recurrence were searched and found. For instance, the presence of ED in the EEG, age, history of febrile seizures, nocturnal seizures, psychiatric comorbidity, history of stroke, and use of ASM are important risk factors. However, age group, use of ASM, and ED presence in the ambulatory EEG were found to be statistically significant,

taking into account that the main purpose of this research was to find the association between the presence of ED in the ambulatory EEG and seizure recurrence. On the other hand, we did not find that other significant risk factors such as stroke, psychiatric comorbidity, febrile seizures, generalized seizures (vs. focal seizures), family history of epilepsy, brain trauma, and developmental delay were significant. We may explain this phenomenon as a result of the age groups analyzed and the purposes of this research. While previous studies have included children and adults, the current study included adults and elderly individuals(78). Some authors have already noted the lack of studies of seizure recurrence after FSUS that include the elderly population (>60 years of age) (18,78,79). In this cohort study there were 21 individuals older than 60 years of age who were compared to the younger group (17-60 years of age). In the bivariate analysis, individuals older than 60 years old had a non-significant hazard ratio of 0.74(95%CI: 0.3,1.8) for seizure recurrence, which is similar to the results of Lawn et al. (18), taking into account that this research had a follow-up of one year. However, in the multivariate analysis, we found that this variable was a confounder in the association between seizure recurrence and the presence of ED in the ambulatory EEG. This phenomenon is demonstrated statistically in Table 5.8, showing changes between unadjusted and adjusted β's (Figure 5.6 and Table 5.9) and discussed in the results section; thus, it should be controlled as we did in the Cox regression analysis. Furthermore, in the final Cox regression model, individuals older than 60 years were found to be statistically less likely to present seizure recurrence, which is a phenomenon seen previously in case-control and cohort studies addressing risk factors for seizure recurrence in an elderly population (18,54). Age as a confounder was supported as it fulfilled criteria for confounding as follows: a wide variety of normal and abnormal EEG patterns can be seen in different age groups (children, adults, and elderly) (37). Also, there are differences in the frequency

of seizure recurrence among different age groups (16). Finally, its distribution across the exposure (ED in the ambulatory EEG) can not be determined by the exposure or by the outcome (seizure recurrence).

Another confounder found was the use of ASM. This is likely the result of the current management of FSUS (surrogate variable). As research has shown, the use of ASM reduces the occurrence of seizures (60). Thus, when the individual is evaluated by the epileptologist/neurologist and the clinician considers the patient is at high risk of recurrence (ED in the ambulatory EEG), the clinician will prescribe ASM. Therefore, the use of ASM (surrogate variable) is associated with both ED in the ambulatory EEG and the seizure recurrence. However, this variable is considered incomplete confounding. The underlying explanatory structure under this confounding is that the use of ASM is associated with both ED in the ambulatory EEG and the seizure recurrence. Nevertheless, ED in the ambulatory EEG is also associated with seizure recurrence (72), see Table 5.9.

The diagnosis of epilepsy in this study was similar to a previous cohort in the same SSC (62), reflecting a referral bias and highly skilled physicians making the diagnosis of epilepsy. We also believe that the use of the last practical definition of epilepsy in the presence of SUS plus EEG abnormalities (14) may have played a role in the high diagnosis of epilepsy. Another weakness of this study was the short follow-up time. The ideal study would include the ambulatory EEG after FSUS and follow-up to 5 years. With this follow-up, we could explore longer-term seizure recurrence in individuals with ED in the ambulatory EEG that did not present with seizure recurrence initially but were initiated on ASM (based on medical history and imaging) as it is well known that the use of ASM significantly delays the risk of relapse (80).

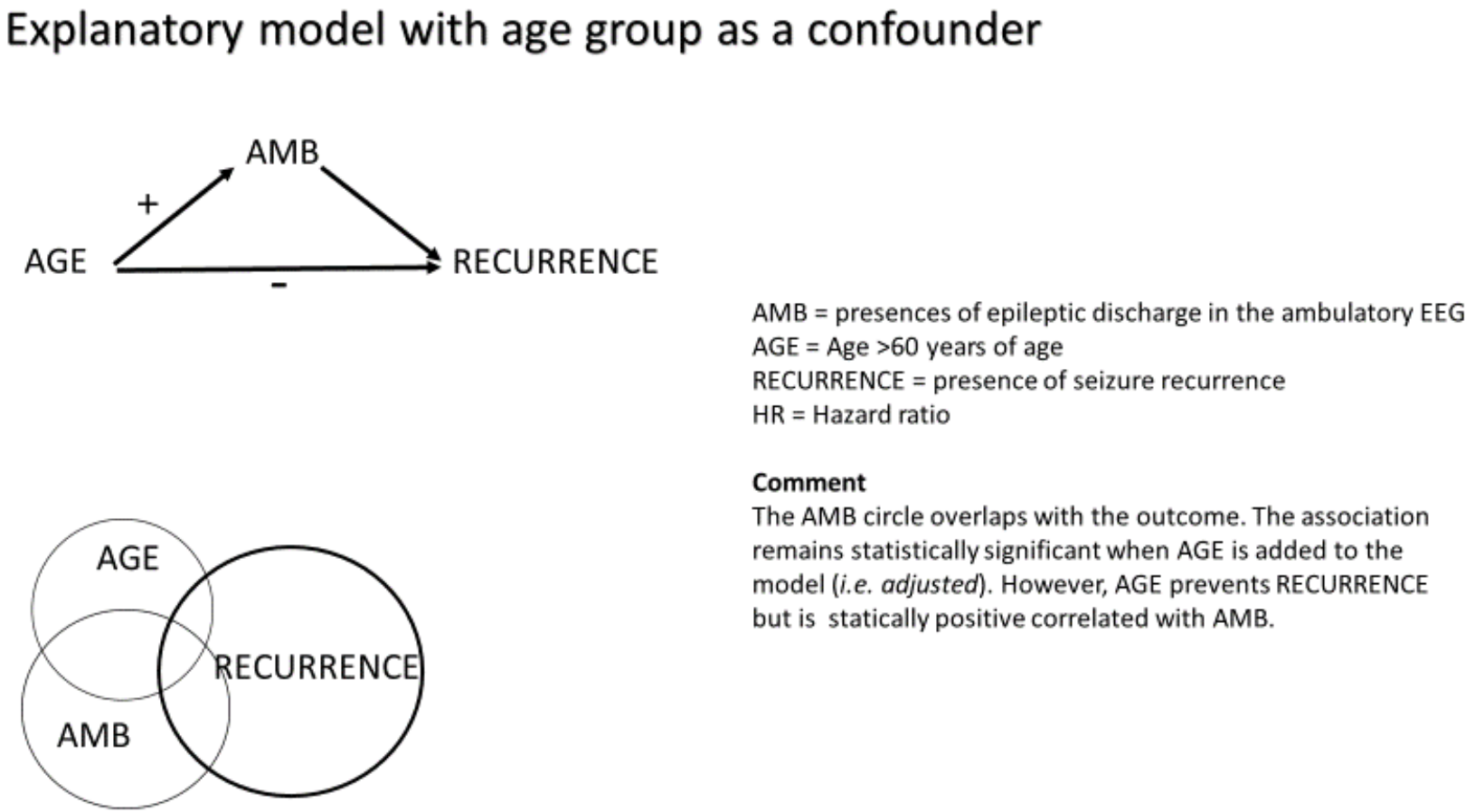
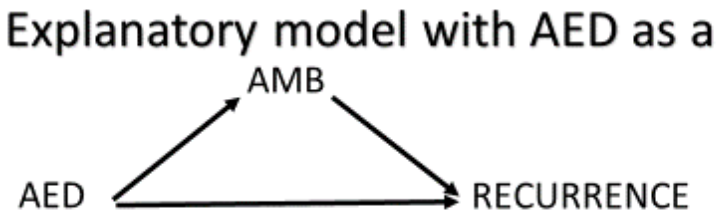
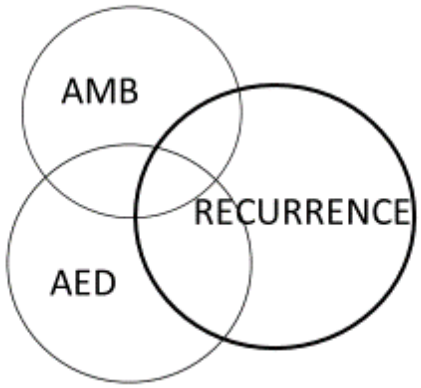


Figure 5.7 A diagram depicting the explanatory model of the association between the presence of epileptic discharge in the ambulatory EEG and seizure recurrence adjusted by age group >60 years old

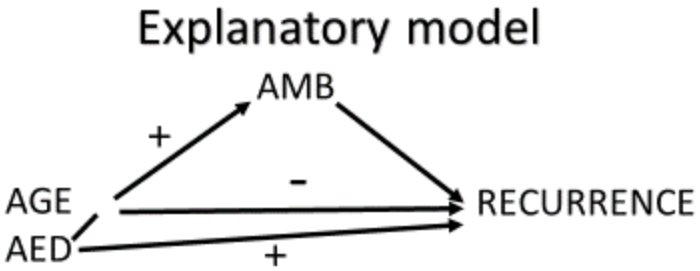


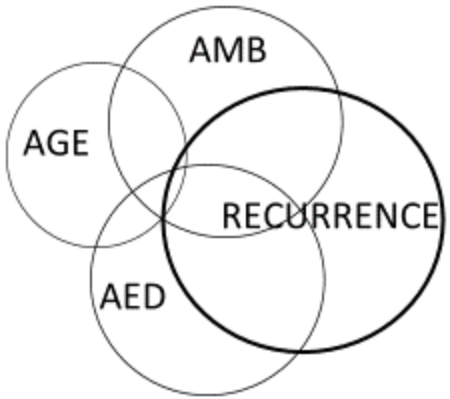
AMB = presences of epileptic discharge in the ambulatory EEG
AED = use of antiepileptic drugs
RECURRENCE = presence of seizure recurrence
HR = Hazard ratio



Comment
The AMB circle overlaps with the outcome. The association remains statistically significant when AED is added to the model (*i.e. adjusted*), but some of the previous association is now attributed to AED. Thus, the AMB-RECURRENCE association is not as strong when AED is controlled as when it was not included. Adding AED to the model explains more of the variation in RECURRENCE than just knowing AMB status.

Figure 5.8 A diagram depicting the explanatory model of the association between the presence of epileptic discharge in the ambulatory EEG and seizure recurrence adjusted by the use of antiseizure medication





AMB = presences of epileptic discharge in the ambulatory EEG
AGE = Age >60 years of age
AED= Use of Antiepileptic Drugs
RECURRENCE = presence of seizure recurrence
HR = Hazard ratio

Comment
The AMB circle overlaps with the outcome. The association remains statistically significant when AGE and AED are added to the model (*i.e. adjusted*). However, AGE prevents RECURRENCE. AGE and AED are causally and statically positive correlated with AMB but AED explains more of the variation in RECURRENCE than just knowing AMB status.

Figure 5.9 A diagram depicting the final model of the association between the presence of epileptic discharge in the ambulatory EEG and seizure recurrence adjusted by the use of antiseizure medication and age group >60 years old.

6.2 Conclusion

This was a pragmatic, prospective, hospital-based clinical study comparing the worldwide gold standard for the diagnosis of epilepsy (first rEEG) and a frequently used modality of repeated rEEG (second EEG) with a low cost and longer recording modality of EEG (ambulatory EEG), finding an improved sensitivity and better negative predictive value for the ambulatory EEG than the first rEEG and second EEG. Overall, the ambulatory EEG was shown to be a better diagnostic test for the diagnosis of epilepsy than rEEG's. In this research, we investigated known risk factors for seizure recurrence in individuals presenting with FSUS, such as stroke, febrile seizures, family history of epilepsy, and age group. We confirmed that the presence of ED was a significant factor in the presence of seizure recurrence at 52 weeks. However, the clinical evaluation of the patient by a specialist (epileptologist/neurologist) remains fundamental in assessing individuals with FSUS. Also, the use of ambulatory EEG can be used in high-income countries and in low-income countries around the world where specialized epilepsy units are not available and replacing then less accurate routine EEG.

Further research with longer follow-up and population-based studies, including the pediatric population, will help clarify the ambulatory EEG's benefits in the general population. Moreover, future studies should control for and compare differences between specialist and non-specialist assessments.

Any effort to improve diagnostic test for the diagnosis of epilepsy will reduce diagnostic errors and reduce the social and psychological stress around newly epileptic individuals and their families and friends.

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