CHARACTERIZING DRUG-RESISTANCE
IN ADULTS WITH NEW-ONSET EPILEPSY

A Thesis Submitted to the College of
Graduate and Postdoctoral Studies
In Partial Fulfillment of the Requirements
For the Degree of Master of Science
In the College of Medicine
University of Saskatchewan
Saskatoon

By

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Abstract

Background and objectives: There are very few studies reporting the factors involved in or the rate of drug-resistant epilepsy (DRE) in adults with new-onset epilepsy (NOE). This prospective cohort study characterizes DRE and risk factors in a pure adult cohort with NOE or newly diagnosed epilepsy (NDE). There are very few studies reporting the factors involved in or the rate of DRE in adults with NO and NDE. Methods: Patients were selected from a prospective cohort followed between 2011 and 2018 from the Single Seizure Clinic (SSC) in Saskatoon, SK. The SSC sees patients who experience their first seizure and approximately 30% are diagnosed with epilepsy. We identified the following variables and outcomes in the cohort: age, gender, epilepsy type, seizure onset, etiology, epilepsy syndromes, EEG and imaging outcomes, and the rates of DRE. Inclusion criteria included patients with NO and NDE, age 18 years or older at time of diagnosis, and a minimum 1 year of follow-up. Results: Ninety-five patients were included, 46 females and 49 males. Median age of onset was 33 years. Of those, 20.0% developed DRE between 2011-2018. Average time between onset and DRE diagnosis was 2.32 years. Bivariate analysis identified age, gender, and etiology as important risk factors for DRE, however these variables failed to be significant in the multivariate model. Discussion: A lower percentage of DRE was identified in this cohort of adults compared to any other published study at present. The majority of patients to develop DRE were diagnosed in the first year of follow up, showing the importance of early characterization and treatment. Similarly, a younger age of onset was shown to be a substantial indicator of the prognosis. Despite a small cohort and insignificant statistical outcomes, our findings might guide the directions of future research in this topic. Significance: The specificity of the cohort along with the outcomes identified in this study contribute valuable information about NOE in adults and the development of DRE. This
study has laid the groundwork for not only a larger cohort study to be implemented in the future, but also several other studies to evaluate potential predictors such as specific imaging results as a risk factor for DRE and quality of life assessment through follow-up related to DRE risk.
Acknowledgements

I would like to give endless thanks to my supervisor Dr. Tellez-Zenteno. From his undying support, countless letters written, battles fought, and successes over this journey, I would not be half the person and academic I am today without him. He always encouraged me to take on new opportunities in research and in education. He was a fundamental part of my entrance to the College of Medicine MD program. Without his guidance and support, this project could not have started.

I would like to thank Dr. Hernandez-Ronquillo, who spent countless hours as a teacher and mentor to me. Her door was always open to answer questions about statistics, research questions, and life. Her care and support for not only this project, but for me and this research team is a shining example of the wonderful person she is.

I would also like to thank Dr. Peña-Sanchez, faculty of the College of Medicine, as my committee chair, and my committee members Dr. Thorpe and Dr. Kirk. Your insight, patience and valuable help with this project was essential to its success.

Finally, I must thank all the teachers and doctors in the College of Medicine at the University of Saskatchewan for your role in teaching, assisting, and advising my education efforts over the years.

Thank you.

Author

Alyssa Denton
Dedication

The completion of another chapter of my education could not have been done without my wonderful support system, inside and outside of academia.

  o To God
  o To my dad and my sister for believing me and being patient with my never-ending pursuit of education.
  o To my adopted family, for showing me boundless love and encouragement.
  o To my friends, for making me persevere in times of deep academic regret.
  o To Doug, Melissa, and Andrea, who taught me who I was and what I was capable of.
  o To Dr. Tellez and Dr. Hernandez-Ronquillo for being a fountain of knowledge and support in my endeavors under their compassionate supervision.
  o And finally, my gratitude to Karen and Pat for being a pivotal part in data collection and helping me survive all my academic endeavors.
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<td>Computed tomography</td>
</tr>
<tr>
<td>DRE</td>
<td>Drug-resistant epilepsy</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IGE</td>
<td>Idiopathic generalized epilepsy</td>
</tr>
<tr>
<td>KM</td>
<td>Kaplan-Meier</td>
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<tr>
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<td>Log-likelihood ratio test</td>
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<td>NDE</td>
<td>Newly-diagnosed epilepsy</td>
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CHAPTER 1: INTRODUCTION

1.1 Background

Epilepsy is a condition that inflicts physical, mental, and social suffering on a growing number of patients diagnosed each year. The understanding of the diagnosis, prognosis, and treatment of epilepsy continues to develop in research today. Epidemiological research of epilepsy contributes to our understanding of the role of epilepsy in population health in Canada and helps us to better support those diagnosed with the condition. Epidemiology aims to add valuable information to the distribution of the condition and improve the consistency of care between physicians who treat patients presenting with new-onset seizures.\(^1\)

The time taken to confirm a diagnosis and initiate treatment is an important contributor to the patient’s quality of life and prognosis. It is well understood at present that there are a variety of socioeconomic, psychosocial, psychiatric, and physical comorbidities associated with epilepsy.\(^2\) The onset of recurrent seizures may derail a sense of stability a patient previously had and can bring on intense feelings of apprehension and anxiety. This has resulted in an ever-expanding interest in the first seizure and its implications in diagnostic outcomes with the goal of easing the mind of the patient. The clinician is key in providing the most recent and relevant information about new-onset epilepsy and associated prognosis.\(^3\)

A major outcome for epilepsy is drug-resistance. A diagnosis of DRE is associated with a poor prognosis for patients, so current research is directed at characterization of patients prior to and after drug-resistance development to enable better prediction and management of the condition. The risk of DRE development in adults with new-onset epilepsy has not been established. The first year after onset is likely to be the most crucial to the prognosis of the condition, with
predictors of DRE including seizure frequency and lesions, particularly hippocampal sclerosis.\textsuperscript{4,5} However, the uncertainty of the underlying pathophysiology makes it difficult to provide a confident prognosis early on.\textsuperscript{5} In the first year, a physician can assess compliance to drug regimens, response to drugs, and changes in seizure characteristics to get a better idea of the complexity of each patient’s individual presentation. Each patient has unique qualities in their epilepsy presentation and variable responses to treatment regimens, further contributing to a difficult prognosis.

Studying the epidemiology of new-onset and DRE rooted in specific age populations will improve our understanding of the relationship between seizures and age groups. Thereby patient care can then be tailored accordingly despite the lack of understanding of the physiology of DRE. This is particularly important in non-pediatric populations, as much of the epidemiology of epilepsy has focused on pediatric populations.

A review of the literature on the topic of NOE and DRE development can be divided into the following categories: an overview of NOE by age group, percentage of DRE in NOE cases by age group, and risk factors for DRE in NOE cases by age group. Although most authors in our literature review categorized children as 0-18 years of age, adults 18-65 years of age, and older adults 65 years or older, some studies have categorized age groups differently. All the literature reviewed prior to January 2017 used the 1981 International League Against Epilepsy classification of epilepsies or similar definitions.\textsuperscript{6} This literature review uses accepted terminology established by the ILAE in January 2017.\textsuperscript{7,8} For specific definitions used, see section 2.1.2.
1.1.1 New-onset epilepsy: an overview

Epilepsy can develop at any age from a plethora of reasons. About 8% of the population will experience a single seizure in their lifetime and 2% of the population will go on to develop epilepsy.\textsuperscript{9,11} Trying to prognosticate NOE is a challenging endeavor for clinicians given the limited understanding of the underlying pathophysiology of epilepsy. Furthermore, the epidemiology of NOE in adults is a relatively new area of study. Understanding the incidence, risk factors, etiology, and essential characteristics of this disorder is crucial to prognosis and counselling of patients with NOE.

The available literature indicates that the overall incidence of epilepsy in developed nations is 44/100 000 person-years.\textsuperscript{10-13} The incidence of NOE is slightly higher in males.\textsuperscript{10,11,14} The incidence of NOE varies by age group, with studies indicating that there is an increased risk for epilepsy development in early childhood and later years of life.\textsuperscript{11-13} The onset of epilepsy is highest in the first year of life, although the aging of the population over time has resulted in proportionately less childhood-onset epilepsy.\textsuperscript{15} As life expectancy has increased, the incidence of epilepsy in the older adult population has also gradually increased, shifting the age-related incidence rates and the associated etiologies.

The few studies that did evaluate NOE across all age groups agreed that: focal onset seizures predominated, the most common epilepsy type was focal with impaired awareness, and the majority of cases had an unknown etiology.\textsuperscript{10,11,14} The large percent of unknown etiologies may be related to the years in which these cases were analyzed and the available technology at the time. For those with a known or presumed etiology, the most common etiologies in children were birth-related events or deficits. In adults the more common etiologies included cerebrovascular disease, CNS infection, CNS tumor, head trauma, and deficits from birth.\textsuperscript{10,11,14}
There is conflicting evidence regarding the association of specific age groups and types of epilepsy. In general, the first year of life is more associated with focal onset epilepsy, the older childhood years and adult years have varying but similar rates of focal and generalized epilepsies, and the older adults have significantly higher rates of focal epilepsies.\textsuperscript{10,11}

Understanding the association of NOE presentation by age is a key component in establishing a prognosis for the disorder, if age does in fact play a role in epilepsy progression. Differences between characteristics and outcomes of NOE versus NDE have not been fully explored and should be a focus of future research, as the inherent timelines associated with their definitions may be an important factor to consider with prognosis.

1.1.2 Percentage of drug-resistant epilepsy in NOE cases in developed countries

Drug-resistant epilepsy (DRE) is an unfortunate outcome in many cases of NOE. Describing the trends for drug-resistance development in NOE is a difficult task given the undefined time factor in the definition of NOE. The consensus of several studies is that 30\% of epilepsy cases do not obtain remission with antiepileptic drug (AED) regimens.\textsuperscript{5,16,17} Establishing a timeline between NOE and DRE development with a corresponding analysis of risk factors is a crucial next step forward in our understanding of NOE prognosis.

Studies that specifically documented the percentage of DRE in NOE in children under 16 years published results ranging from 10\% to 29\% drug-resistance.\textsuperscript{18,19} Average follow-up time in these studies varied from 5-8 years, providing adequate illustration of epilepsy progression from point of diagnosis. Studies including both older children and adults (9-93 years) indicate that about 25-37\% do not reach seizure free states.\textsuperscript{20,21} There is no literature at present to evaluate the rate of DRE specifically in younger or older adults with NOE.
1.1.3 Risk factors for DRE in NOE in developed countries

Evaluation of pre-ictal and intra-ictal seizure characteristics is essential to the diagnosis and prognosis of epilepsy cases. Components of seizures such as mode of seizure onset, awareness, seizure type, etiology, syndrome, seizure frequency, and response to AEDs have been identified as indicators of the severity of the disorder and how well the patient will respond to different treatment regimens. Sex has not been indicated in literature as being a confounding factor in the development of DRE.

Seizure mode of onset (generalized, focal, or combined onset based on EEG or neuroimaging studies) differs from epilepsy type and may play a key role in epilepsy prognosis.\(^7\) A generalized mode of seizure onset has been shown to be associated with a higher risk of drug-resistance in pediatric cohorts.\(^{18,22}\) Those with focal onset seizures were more likely to fail AEDs if the seizures were characterized with impaired awareness in a pediatric population.\(^{19}\) The relationship between mode of onset and epilepsy outcomes have not been evaluated in adults or older adult populations. The evaluation of mode of seizure onset as a variable separate from epilepsy type is inconsistent in the literature, since it did not have a well-established definition until the new ILAE standards in 2017.

In follow-up studies starting with the time of NOE diagnosis, focal epilepsy type with unknown or structural etiologies were found to be the most associated with a poor outcome in both children and adult cohorts.\(^{16,18,20,21}\) These results are in contrast to a generalized epilepsy type with or without a presumed genetic etiology (commonly described in literature as an idiopathic etiology based on the ILAE 1981 definition of epilepsy) having a worse prognosis in children.\(^6\)
Evaluating etiology is likely to play a key role in prognosticating NOE. Literature shows that epilepsy due to mesial temporal sclerosis (MTS) leads to DRE in 42-67% of cases and is more commonly associated with DRE in comparison to other etiologies.\textsuperscript{23,24} Brain tumors, specifically benign, have been shown to be an underlying factor in DRE development, and in some types of tumors drug-resistance is particularly likely.\textsuperscript{25,26} No such studies were found regarding etiologies such as arteriovenous malformation, cerebral infarction, cerebral atrophy, or cortical dysplasia. The evaluation of the incidence of DRE in specific etiologies is under evaluated at present and might be a focus of future research.

The evaluation of outcomes for epileptic syndromes have been studied in pediatric cohorts,\textsuperscript{27} however there was no literature found to assess epilepsy syndromes as a risk factor for DRE development in adults with NOE. This is likely due to the fact that genetic syndromes and self-limiting focal syndromes more commonly begin in childhood.\textsuperscript{8} Given the purpose of this review, we felt it unnecessary to highlight pediatric-specific syndrome outcomes.

The number of seizures and time intervals between seizures is possibly indicative of how the epilepsy disorder will progress in adult patients with NOE. Both pediatric and all age cohorts have identified that a higher number of seizures prior to the commencement of AEDs is indicative of the severity of an individual’s epilepsy disorder.\textsuperscript{21} The frequency of seizures and the time periods between episodes are significantly associated with DRE development in both children and adults; patients with two seizures prior to diagnosis who developed DRE later on had an average time interval of 0.5 months between the first two seizures, and those who did not develop DRE had an average time interval of 4.7 months.\textsuperscript{18} Similarly, one study found that the longer the length of a seizure free interval in the first two years of follow-up was a predictive
factor in establishing seizure remission.\textsuperscript{16} Such findings strengthen the hypothesis that time is a key factor in DRE development in one way or another.

Not only are such risk factors possibly influencing a poor response to AEDs but failing the first AED regimen has also been shown to be an independent risk factor for DRE development in all age categories, further supporting the need for a timely, informed diagnosis and treatment plan.\textsuperscript{19-22,28,29}

Patients of any age are at risk for developing DRE. Studies specific to NOE and the progression to DRE are limited, especially in adult populations. The necessity of detailed risk factor associations for adult NOE patients is crucial for being better prepared for DRE development.

All literature reviewed via a search of key words in PubMed: new-onset epilepsy, drug-resistant epilepsy, mesial temporal sclerosis, epilepsy, and seizures.

1.2 Statement of the problem

About 8\% of the population will experience a single unprovoked seizure in a lifetime but only approximately 2\% of the overall population will go on to develop epilepsy.\textsuperscript{9,11} The point prevalence of epilepsy in Canada is 5-6 per 1000 people with an age-standardized incidence of 62 per 100 000 person-years in Saskatchewan.\textsuperscript{30,31} For indigenous persons, the age standardized incidence of epilepsy is 122 per 100000-person years, almost double the general population rate of epilepsy.\textsuperscript{31} There is a 40-52\% risk of recurrence after the first unprovoked seizure and a 73\% (95\% CI 59-87\%) risk after the second unprovoked seizure that is more than 24 hours later.\textsuperscript{32}

The impact of this condition on normal functioning is so significant that it is worked into the conceptual definition of epilepsy:
An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychosocial, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.\textsuperscript{32}

The consensus of several studies is that 30\% of epilepsy cases do not obtain remission via antiepileptic drug (AED) regimens.\textsuperscript{5,16,17} The estimated incidence of DRE occurring in new-onset epilepsy patients varies due to studies skewed towards the pediatric epilepsy population, which prevents generalization to all age groups. Treatment options after established DRE include vagal nerve stimulation, deep-brain stimulation, and epilepsy surgery, each of which carry their own set of possible adverse effects and outcomes. Having a more thorough understanding of DRE will lead to more informed decision-making regarding treatment with the intention of reducing adverse outcomes for patients.

1.3 Purpose and objectives

The purpose of this study is to characterize drug-resistance in cases of new-onset and newly-diagnosed epilepsy in an adult cohort from the Single Seizure Clinic (SSC) in Saskatchewan, Canada. This study seeks to quantify characteristics relevant to the development of DRE in adults with NOE over a 6-year period: Nov. 2011 – Jan. 2018. The specific objectives for characterizing DRE in adults with new-onset/newly-diagnosed epilepsy are:

1. Identify the association between demographic characteristics and DRE development.
2. Identify the association between epilepsy type and DRE development.
3. Identify the association between etiology and DRE development.
4. Identify the association between epilepsy syndromes and DRE development.

5. Identify the association between seizure clinical features and DRE development.

6. Evaluate the average time from first seizure to DRE diagnosis (excluding provoked seizures).

1.4 Research questions

1. What percentage of adults with new-onset or newly-diagnosed epilepsy will develop drug-resistance?

2. What are the associations between the development of DRE and key independent variables (demographic characteristics, epilepsy type, seizure type, seizure clinical features, epilepsy syndromes, and etiology)?

3. In a population of adults which develop DRE, what is the average time between first seizure and a diagnosis of DRE?
CHAPTER 2: METHODS

2.1 Study Population

Patients are residents of Saskatchewan, one of the 13 provinces and territories in Canada. Saskatchewan has an estimated population of 1,163,925 as of July 1st, 2017 with 50.3% being female and 49.7% being male. People aged 15 years and over make up 80.3% of the population. According to the 2011 National Household Survey, 76.0% of Saskatchewan residents claim European descent, 6.3% claim to be a visible minority, and 15.6% self-identify as indigenous. This is the second highest indigenous population in Canada, following the adjacent prairie province, Manitoba. About a quarter of the population lives in and around Saskatoon.

Our cohort was selected from a pre-existing cohort from the SSC at the Royal University Hospital in Saskatoon, Saskatchewan. The SSC opened in 2011 and provides care to patients from all over the province who have been referred from other medical professionals for suspicion of seizures. The clinic primarily sees adult patients (18+ years). All referred patients receive a standard twenty-minute EEG prior to the consultation in the SSC. If the EEG is unremarkable and neuroimaging is normal or unavailable, then the patients are given a 24-hour ambulatory EEG if the neurologist feels it will aid in the diagnostic process. A sleep-deprived EEG may also be requested.

This study was approved by the Biomedical Research Ethics Board at the University of Saskatchewan (Bio#12-039).
2.1.1 Data sources

The study utilized pre-existing patient files from the SSC and hospital health records. Data were assessed using a customized data abstraction tool. All procedures were consistent with the accepted standards for epidemiologic studies.36

2.1.2 Cohort case definition algorithm

To build a prospective cohort study, adult patients (18+ years at diagnosis) residing in Saskatchewan with a minimum of 1-year follow-up time after the first appointment at the SSC were entered into the cohort. Patients required a formal diagnosis of epilepsy at some point in the follow-up with no previous diagnosis or treatment of a seizure disorder.

The operational definition of epilepsy applies to patients identified after the second seizure (>24 hours apart), patients identified after one seizure with a risk of recurrence similar to that of patients after their second seizure (≥60%), or patients diagnosed with an epilepsy syndrome.32 This is the most updated version of the definition for epilepsy which is used to identify NOE/NDE patients in the SSC.

The ILAE does not have formal definitions for either new-onset or newly-diagnosed epilepsy. New-onset epilepsy is defined as patients seen after their second seizure, whereas newly-diagnosed epilepsy includes both patients seen after their second seizure and patients with a previously undocumented and untreated history of seizures.36 The incidence of newly-diagnosed epilepsy is presumed to be higher than that of new-onset, although corresponding incidence studies have not been assessed in studies. Febrile seizures were not included as a first seizure; however, they were recorded as part of medical history. Patients diagnosed with juvenile myoclonic epilepsy (JME) syndrome were included as NOE or NDE regardless of possible myoclonic jerks existing for years prior to diagnosis, as they rarely lead to neurological
consultation. Also, those included with JME did not have a formal diagnosis of epilepsy until 18 years of age or older, as per our criteria.

Neither of the definitions for new-onset or newly-diagnosed epilepsy have a time variable, causing uncertainty in the specific categorization of patients. This is a noted flaw in the study with no research at present allowing for a resolution. I defer this issue to a study at a later time.

Three definitions for DRE are used to identify patients with DRE:

1. Kwan and Brodie at 1-year post diagnosis\(^{21}\): Patients who had seizures were by definition considered to have refractory epilepsy. Seizure-free status was defined as the lack of seizures of any type for a minimum of 1 year while receiving the same dose of AED or while not taking any medication.

2. Camfield and Camfield at 1-year post diagnosis\(^{19}\): Patients with an average of two or more seizures in each 2-month period during the last year of observation, despite treatment with at least three AEDs as monotherapy or polytherapy.

3. ILAE after 2 years post diagnosis\(^{37}\): Patients who have failed an adequate trial of two tolerated and appropriately chosen AED regimens to sustain seizure freedom. Seizure freedom is defined by a duration of three times the longest interseizure interval prior to starting a new intervention.

After the first year of follow-up, only the ILAE definition was used to identify the percentage of DRE in the cohort. In the first year, both Kwan & Brodie and the Camfield & Camfield definitions were used as they included a broad spectrum of patients with persisting seizures, as well as categorized patients under more rigorous criteria, respectively. This was necessary because the internationally accepted ILAE definition of DRE is specific to the 2-year follow-up
point and this study aimed to characterize patients in the first year of follow-up as well, therefore two definitions were used to identify patients early, thereby increasing the validity of our concluded rate of DRE. All three definitions were shown to meet criteria for reliability and validity, with the ILAE definition obtaining the highest score for reliability. The ILAE definition for DRE is the internationally accepted definition and no changes have been made to the diagnostic criteria since its publication in 2010.

2.1.3 Independent variable choice and definitions

Independent variables were chosen based on their clinical relevance to describing the cohort and their possible association with the outcome variable as a risk factor. Risk factors were chosen based on prior review of literature (see Section 1.1) and expert opinion. The updated ILAE classification guidelines were used to define epilepsy characteristics, seizure characteristics, epilepsy syndromes, and etiology. Use of the older classification in patient charts were updated accordingly for the study. Within part of the SSC physician form filled out for all patients is a section specifically for describing the most clinically significant medical history that the physician feels are attributable to the seizures. The medical history and clinical features govern the diagnosis of two of the more ambiguous etiologies: cranial trauma and epilepsy associated with dementia. All other etiologies were confirmed with appropriate testing. Abnormal EEG defined by having some form of epileptiform discharges based on expert reports in the chart review. Abnormal imaging implying an identifiable lesion likely to be associated with seizure production, based on expert report in the chart review. Given the short follow-up time period in this study, all data for risk factors was used with the assumption that no significant changes occurred over the 6 years.
2.1.3.1 Independent variable categorization for analysis

All independent variables are nominal, either dichotomous (i.e. abnormal EEG) or categorical (i.e. etiology). Age did not satisfy the assumption of normality and was therefore categorized equally into four groups for analysis. In the bivariate and multivariate analyses, epilepsy type was simplified to include the generalized and focal categories, eliminating the combination category and unknown category to concentrate on essential risk factor groups based on the literature review. Similarly, seizure type was simplified to only include the generalized and focal categories, eliminating the unknown category. No other variables were altered for the analysis.

2.2 Analysis

Statistical analysis was conducted using STATA 15.1 (StataCorp, College Station, TX).

2.2.1 Descriptive Statistics

The frequencies of all categorical variables were calculated as percentages. The mean with standard deviation (SD), median, and range was calculated for continuous variables. For objective #6 specifically, the dates of first seizure, first appointment at the SSC, and date of diagnosis of epilepsy are all found in patient charts. The date of diagnosis of DRE was estimated at the end of the recorded follow-up year, as no specific dates were recorded in patient files for such. The difference in time between first seizure and DRE development were evaluated from these dates using Microsoft Excel.
2.2.2 Statistical Inference

The associations between the independent variables and the outcome variables (DRE development) were evaluated for the entire follow-up period of six years. Pearson’s Chi square, or Fisher’s exact test if appropriate, was used to evaluate statistical differences between the group of patients who developed DRE and those who did not develop DRE within the follow-up period. A p-value of 0.05 was used to determine statistical significance.

In order to assess the association between risk factors and the development of DRE over time, the Cox Proportional Hazards (PH) model was used. The survival time was measured in months. Patients without DRE were censored after follow-up ended or death occurred. Censorship implied that some information was known about the patient’s condition progression, but the exact time survived without the event (DRE) was unknown. This process is referred to as right censorship, as censoring occurs to the right of the follow-up time interval.

The PH model assumes that any two specifications of a predictor variable are constant over time. Two graphical methods and one quantitative method were used to assess this assumption: Kaplan-Meier (KM) survival predictability curves, log-log survival curves, and the Goodness of Fit (GOF) test. The curves were generated for categorical variables from the start of follow-up to the time of event or censorship. Both the Kaplan-Meier method and log-log survival curves provide step-functions that allow for analysis of survival between groups at different points of time. The log-log survival curves should have a constant vertical difference between the two groups over the length of follow-up. The Kaplan-Meier observed and predicted curves should close together for the PH assumption to be satisfied.

The quantitative assessment of the PH assumptions was completed with the GOF test. The GOF test was generated with each bivariate analysis using a p-value of 0.05. Test results
with a p-value greater than 0.05 indicate that there is no significant difference between the hazards in a model with and without the independent variable, so the PH assumption is met. Both the subjective and objective methods of assessing the PH assumption are important for evaluating the validity of the independent variables in hazard analysis for DRE.

A bivariate analysis was conducted for all variables (Table 2.1). Hazard ratios are produced in this method, which describes the hazard function as the potential for an event to occur per unit of time.\textsuperscript{40} Within the survival analysis the survival probability decreases as the hazard rate increases. Variables chosen to be included in the multivariate model had a p-value $\leq 0.25$.\textsuperscript{41} The Efron method for handling ties in the data set was used.\textsuperscript{42}

A backward stepwise model building process was used to establish a final multivariate model. The log-likelihood ratio test (LRT) was used to either keep or eliminate covariates from the model depending on how they influenced the model’s overall HR:

$$LRT = [-2 \text{ log-likelihood (reduced model)}] - [-2 \text{ log-likelihood (full model)}]$$

\textit{(Equation 1)}

For this procedure a p-value of 0.05 was used. Age of onset and sex were both assessed as confounders using the following equation:

$$\frac{(\text{Crude HR} - \text{Adjusted HR})}{\text{Crude HR}}$$

\textit{(Equation 2)}

A result greater than 10% would be considered a significant confounder in the model.
Based on clinical relevance, the interaction terms age of onset with etiology (age*etiology) were assessed with the multivariate model for significant effects on the dependent variable.
Table 2.1: List of variables to be assessed for statistical significance in developing DRE using the cox proportional hazards model.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CODING^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVENT</td>
<td>DRE (1)</td>
</tr>
<tr>
<td></td>
<td>CENSORED (0)</td>
</tr>
<tr>
<td>TIME</td>
<td>MONTHS (CONTINUOUS)</td>
</tr>
<tr>
<td>AGE OF ONSET</td>
<td>12-24 years (2)</td>
</tr>
<tr>
<td></td>
<td>25-44 years (1)</td>
</tr>
<tr>
<td></td>
<td>45-82 YEARS (0)</td>
</tr>
<tr>
<td>SEX</td>
<td>Male (1)</td>
</tr>
<tr>
<td></td>
<td>FEMALE (0)</td>
</tr>
<tr>
<td>ABNORMAL EEG</td>
<td>Yes (1)</td>
</tr>
<tr>
<td></td>
<td>No (0)</td>
</tr>
<tr>
<td>ABNORMAL NEUROIMAGING (CT AND/OR MRI)</td>
<td>Yes (1)</td>
</tr>
<tr>
<td></td>
<td>No (0)</td>
</tr>
<tr>
<td>EPILEPSY TYPE</td>
<td>Generalized (1)</td>
</tr>
<tr>
<td></td>
<td>FOCAL (0)</td>
</tr>
<tr>
<td>SEIZURE TYPE</td>
<td>Generalized (1)</td>
</tr>
<tr>
<td></td>
<td>FOCAL (0)</td>
</tr>
<tr>
<td>ETIOLOGY^b</td>
<td>Cranial Trauma (5)</td>
</tr>
<tr>
<td></td>
<td>Masses (4)</td>
</tr>
<tr>
<td></td>
<td>MTS (3)</td>
</tr>
<tr>
<td></td>
<td>Stroke (2)</td>
</tr>
<tr>
<td></td>
<td>Cortical Dysplasia (1)</td>
</tr>
<tr>
<td></td>
<td>UNKNOWN (0)</td>
</tr>
<tr>
<td>EPILEPSY SYNDROME</td>
<td>JME (2)</td>
</tr>
<tr>
<td></td>
<td>GTCS alone (1)</td>
</tr>
<tr>
<td></td>
<td>NONE (0)</td>
</tr>
</tbody>
</table>

a. Lowest value used as reference category in STATA.

b. The etiologies AVM, dementia, and limbic encephalitis with zero patients in the DRE category were excluded from the list as STATA automatically does not include them Cox regression analysis.
3.1 The percentage of DRE in an adult population with NOE/NDE

3.1.1 Overall percentage of DRE

An analysis of all adult patients referred to the SSC in Saskatchewan between November 1st, 2011 and January 31st, 2019 revealed 95 patients diagnosed with epilepsy with at least one year of follow-up with a neurologist. The patient cohort is described in Tables 3.1 and 3.2. Of the 95 patients, 30 (31.6%) were diagnosed with DRE by any of the three definitions at some point within the 6 years of available follow-up. Only 19 (20.0%) patients met our criteria for DRE.
Table 3.1: General characteristics of adults with new-onset epilepsy in Saskatchewan (N = 95)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%) / mean (SD), median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (51.6)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (48.4)</td>
</tr>
<tr>
<td><strong>Age at last follow-up (years)</strong></td>
<td>41.3 (19.2), 36 (18–83)</td>
</tr>
<tr>
<td><strong>Age at onset of seizures (years)</strong></td>
<td>38.7 (19.3), 33 (12–82)</td>
</tr>
<tr>
<td><strong>Follow-up time (years)</strong></td>
<td>2.5 (1.4), 2 (1–6)</td>
</tr>
<tr>
<td><strong>Location in Saskatchewan</strong></td>
<td></td>
</tr>
<tr>
<td>Saskatoon</td>
<td>51 (53.7)</td>
</tr>
<tr>
<td>Other</td>
<td>44 (46.3)</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
</tr>
<tr>
<td>Head Trauma</td>
<td>25 (26.3)</td>
</tr>
<tr>
<td>Family History</td>
<td>17 (17.9)</td>
</tr>
<tr>
<td>Brain Tumor</td>
<td>8 (8.4)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>CNS Infection</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Status Epilepticus</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Febrile Seizures</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>None</td>
<td>26 (27.4)</td>
</tr>
</tbody>
</table>
Figure 3.1 The distribution of age at onset in a cohort of adults with new-onset epilepsy.
Table 3.2: Characteristics of epilepsy in adults with NOE in Saskatchewan.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epilepsy Type</strong></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>37 (38.9)</td>
</tr>
<tr>
<td>Focal</td>
<td>51 (53.7)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (1.05)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td><strong>Seizure Type</strong></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>47 (49.5)</td>
</tr>
<tr>
<td>Focal</td>
<td>47 (49.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td><strong>Location of Focus</strong></td>
<td></td>
</tr>
<tr>
<td>Right Temporal</td>
<td>14 (14.7)</td>
</tr>
<tr>
<td>Left Temporal</td>
<td>28 (29.5)</td>
</tr>
<tr>
<td>Extratemporal</td>
<td>10 (10.5)</td>
</tr>
<tr>
<td>Non-focal/Unknown</td>
<td>43 (45.3)</td>
</tr>
<tr>
<td><strong>Identified etiologies</strong></td>
<td></td>
</tr>
<tr>
<td>Mesial temporal sclerosis</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Cranial trauma</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Benign Cerebral Neoplasm</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Malignant Cerebral Neoplasm</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Cortical Dysplasia</td>
<td>2 (7.14)</td>
</tr>
<tr>
<td>Arteriovenous Malformation</td>
<td>2 (7.14)</td>
</tr>
<tr>
<td>Choroidal fissure cyst</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Associated with Dementia</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td><strong>Syndrome Classification</strong></td>
<td></td>
</tr>
<tr>
<td>GTCS</td>
<td>30 (31.6)</td>
</tr>
<tr>
<td>Juvenile Myoclonic Epilepsy</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>None</td>
<td>60 (63.1)</td>
</tr>
</tbody>
</table>

a. Epilepsy type is determined by EEG and/or imaging studies, b. Seizure type based on ILAE 2017, GTCS: Generalized tonic clonic syndrome
3.1.1.1 Percentage of DRE by year of follow-up

The majority of diagnoses of DRE were made in the first year of follow-up (N=22, 23.9%, [Table 3.3]). Not all of those diagnosed in the first year remained drug-resistant by the ILAE criteria in later years (see section 3.1.1.2). There was no pattern to the percent diagnosed per year or how many remained diagnosed in each year of follow-up. In the second and fourth years, one new patient was diagnosed with DRE in each year. Year 5 had two new patients diagnosed with DRE. Years 3 and 6 had no DRE diagnoses.

3.1.1.2 Percentage of DRE by definition

A total of 30 (31.6%) of patients were diagnosed with DRE by the Kwan & Brodie definition. Twenty-two patients in year 1 met these criteria. Of those 22 patients, 6 were censored after the first year and 7 did not meet the criteria in later follow up. Four new patients met the criteria for DRE at year 2, three patients in year 3, and one patient in year 4. There were no new diagnoses of DRE by this definition in years 5 and 6 of follow-up. There was inconsistent follow-up for 5 patients in that they either had 1 or 2 years missing of follow-up consecutively at some point within the 6 years.

For the Camfield & Camfield definition of DRE, a total of 10 patients (10.5%) were diagnosed at some point in the 6 years of follow-up, however only 7 remained drug-resistant by this definition in the last year of follow-up. Five patients were diagnosed in the first year, 4 new patients in the second, and 1 new patient in the 3rd year of follow-up. Of the 5 in the first year, 3 were censored after the first year, 1 was not considered DRE in the second year and 1 was not considered DRE by the 4th year. Of the 4 diagnosed in their second year, 2 were censored after year 2, 1 remained drug-resistant through follow-up, and one was not considered drug-resistant.
at final follow-up. The patient diagnosed in their third year (no follow up appointments in year 1 and 2) remained drug-resistant for the following 3 years of follow-up. There were 3 patients who were not considered drug-resistant by this definition at their last follow-up appointment, but they were still considered drug-resistant by Kwan & Brodie definition, thus indicating that they were still having seizures, just not within the very specific time frame put forth by the Camfield & Camfield definition.

For the ILAE drug-resistant analysis, 13 patients met this definition criteria at some point in the follow up from the 2nd year onwards. This is 13.7% of the total cohort. Of the 13 patients, 9 were diagnosed in year 2 (first available point assessment by this definition). Of those 9, only 1 was not considered DRE by the end of follow up and this was in their fifth year of follow-up. One patient was diagnosed in year 3 and remained DRE for the remainder of FU (same patient with no follow-up in first 2 years as mentioned above). Three patients were not diagnosed until year 5; they were considered DRE by Kwan & Brodie definition but not ILAE in the prior 4 years of follow up.

Table 3.3: Number of patients with DRE in each year of follow-up by definition (%).

<table>
<thead>
<tr>
<th>Year 1 (N=92)</th>
<th>Year 2 (N=64)</th>
<th>Year 3 (N=40)</th>
<th>Year 4 (N=17)</th>
<th>Year 5 (N=12)</th>
<th>Year 6 (N=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILAE</td>
<td>9 (14.1)</td>
<td>6 (15.0)</td>
<td>2 (11.8)</td>
<td>4 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Kwan &amp; Brodie</td>
<td>22 (23.9)</td>
<td>15 (23.8)</td>
<td>10 (25.0)</td>
<td>4 (23.5)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Camfield &amp; Camfield</td>
<td>5 (5.4)</td>
<td>5 (7.9)</td>
<td>3 (7.5)</td>
<td>1 (5.9)</td>
<td>1 (8.3)</td>
</tr>
</tbody>
</table>

ILAE = International League Against Epilepsy
3.1.2 Demographics of patients that developed DRE

Forty-nine (51.6%) of the 95 patients were male, 12 of which developed DRE (p-value = 0.26 [Table 3.4]). Nine of 33 patients had their first seizure between the ages 12-24 years, 5/28 patients between the ages 25-44 years, and 5/34 between the ages 45-82 years. The overall p-value when comparing age of seizure onset of those who developed DRE and those who did not is 0.41.

3.1.3 Epilepsy characteristics in patients who developed DRE

The majority of those who developed DRE had focal epilepsy (12/19 or 63.2%) (Table 3.4). One patient was diagnosed with both focal and generalized epilepsy, and developed DRE. Six patients had an unknown epilepsy type, only one developed epilepsy. The p-value for epilepsy type between the DRE group and non-DRE group was 0.24. In terms of seizure type, there were equally 47 patients with generalized seizures and 47 with focal seizures, although a higher percent developed DRE with focal onset seizures (23.4% versus 17.0%, p = 0.44). One patient had an unknown seizure type and did not develop DRE. Twenty-six patients had abnormal imaging results, either with CT or MRI. Eight of those developed DRE (p = 0.94). Seventy-five patients had abnormal EEG results, 15 of whom developed DRE (p = 0.61).

Of the 95 epilepsy patients, only 28 had a diagnosed etiology. None of the patients with the etiologies stroke, AVM, neurodegenerative disorders, or encephalitis developed DRE. The etiologies cranial trauma and MTS were combined into the term “structural etiology” and compared with all other etiologies in the chi-square analysis. Four of the 9 patients with structural etiology developed DRE (p = 0.05).
Only two epilepsy syndromes were recorded in the cohort: 5 with JME and 30 with GTCS alone, of which 1 and 7 developed DRE, respectively.
Table 3.4: General characteristics of adults with NOE with and without DRE in Saskatchewan (N = 95)

<table>
<thead>
<tr>
<th></th>
<th>No DRE n(%)</th>
<th>DRE n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>76 (80.0)</td>
<td>19 (20.0)</td>
</tr>
<tr>
<td>Age of onset (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-24 years</td>
<td>24 (72.7)</td>
<td>9 (27.3)</td>
</tr>
<tr>
<td>25-44 years</td>
<td>23 (82.1)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>45-82 years</td>
<td>29 (85.3)</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (75.5)</td>
<td>12 (24.5)</td>
</tr>
<tr>
<td>Female</td>
<td>39 (84.8)</td>
<td>7 (15.2)</td>
</tr>
<tr>
<td>Epilepsy type&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>39 (76.5)</td>
<td>12 (23.5)</td>
</tr>
<tr>
<td>Generalized</td>
<td>32 (86.5)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>Seizure type&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal Onset</td>
<td>36 (76.6)</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>Generalized Onset</td>
<td>39 (83.0)</td>
<td>8 (17.0)</td>
</tr>
<tr>
<td>Abnormal imaging (CT or MRI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 (80.8)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>60 (80.0)</td>
<td>15 (20.0)</td>
</tr>
<tr>
<td>Etiology&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural lesion&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (55.6)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;d&lt;/sup&gt;</td>
<td>71 (82.6)</td>
<td>15 (17.4)</td>
</tr>
<tr>
<td>Epilepsy Syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile Myoclonic Epilepsy</td>
<td>4 (80.0)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>GTCS</td>
<td>26 (86.7)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>None</td>
<td>42 (75.0)</td>
<td>14 (25.0)</td>
</tr>
</tbody>
</table>

Chi squares were performed. a. Epilepsy type was determined by EEG and/or imaging studies based on ILAE 2017 guidelines; patients with an unknown type were excluded from this analysis. b. Seizure type was determined by clinical history with definitions based on ILAE 2017 guidelines; patients with an unknown type were excluded from this analysis. c. Combined etiologies cranial trauma and mesial temporal sclerosis. d. Refer to table 2.1 for list of etiologies, GTCS: Generalized tonic clonic syndrome. Data are presented as percentages. *Had a significant p-value
3.2 Evaluating the development of DRE with key independent variables

3.2.1 Bivariate analysis

Eight risk factors were assessed for their association with the development of DRE over time (Table 3.5). A Cox regression bivariate analysis between the dependent variable “event” and independent risk factors revealed three variables that could be further assessed in a multivariate model based on the use of p-value ≤ 0.25: age of onset, sex, and etiology. The category 12-24 years for age of onset had a p-value of 0.21. Male sex was associated with a p-value of 0.24. The category for MTS in etiology had a p-value of 0.15.

3.2.1.1 Survival curves: Kaplan Meier curves

The Kaplan-Meier survival curves (Figures 3.2-3.9) demonstrated stepwise functions for the estimated percent survival at each point of follow-up in the study, both predicted and observed. All curves showed approximately “close” distance between the predicted and observed curves, with the exception of the beginning and end of the curves where there were fewer observations to be evaluated.
Figure 3.2: Kaplan-Meier survival estimates of the risk factor age

Figure 3.3: Kaplan-Meier survival estimates of the risk factor sex.
Figure 3.4: Kaplan-Meier survival estimates of the risk factor epilepsy type.

Figure 3.5: Kaplan-Meier survival estimates of the risk factor seizure type.
Figure 3.6: Kaplan-Meier survival estimates of the risk factor EEG results.

Figure 3.7: Kaplan-Meier survival estimates of the risk factor imaging results.
Figure 3.8: Kaplan-Meier survival estimates of the risk factor etiology.

Figure 3.9: Kaplan-Meier survival estimates of the risk factor epilepsy syndrome.
3.2.1.2 Survival curves: Log-log plots

Log-log plots of the independent variables analyzed in the bivariate cox regression revealed parallel curves between the categories of each independent variable. Non-parallelism recurred for several variables at the beginning and end of each graph, where observations were smaller.

Notable areas of non-parallelism were seen in the independent variable etiology, where MTS and cortical dysplasia crossed near the center of the survival curve. Crossing of categories indicated that the hazards for those etiologies were not proportional over time, similar to the Kaplan-Meier curves.

3.2.1.3 Goodness of fit test

Six of the 8 variable assessed for PH assumptions using the GOF produced p-values > 0.05, indicating no significant differences between the hazards of separate categories for each variable over time. The variables epilepsy type and seizure type produced p-values <0.05 indicating they did not meet the assumption of proportional hazard over time for the involved categories.

3.2.2 Multivariate analysis

Age of onset, sex, and etiology were included in the initial model and a backward stepwise model building strategy was conducted. Sex and etiology were both eliminated with non-significant p-values, leaving a final model with no significant predictors.
Table 3.5: Bivariate and multivariate cox regression models of drug-resistance in adults with new-onset epilepsy in Saskatchewan.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude HR</th>
<th>[95% CI]</th>
<th>Adjusted HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-24 years</td>
<td>2.02</td>
<td>[0.68-6.06]</td>
<td>1.68</td>
<td>[0.53-5.36]</td>
</tr>
<tr>
<td>25-44 years</td>
<td>0.98</td>
<td>[0.28-3.43]</td>
<td>0.92</td>
<td>[0.22-3.91]</td>
</tr>
<tr>
<td>45-82 years</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.75</td>
<td>[0.69-4.45]</td>
<td>1.85</td>
<td>[0.65-5.29]</td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.90</td>
<td>[0.30-2.73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal neuroimaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.78</td>
<td>[0.24-2.51]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTS</td>
<td>2.57</td>
<td>[0.71-9.34]</td>
<td>2.58</td>
<td>[0.70-9.57]</td>
</tr>
<tr>
<td>Cranial Trauma</td>
<td>0.73</td>
<td>[0.09-6.06]</td>
<td>0.72</td>
<td>[0.07-7.78]</td>
</tr>
<tr>
<td>Masses/cysts</td>
<td>0.50</td>
<td>[0.07-3.86]</td>
<td>0.49</td>
<td>[0.06-4.06]</td>
</tr>
<tr>
<td>Cortical Dysplasia</td>
<td>1.56</td>
<td>[0.19-13.0]</td>
<td>2.42</td>
<td>[0.24-24.43]</td>
</tr>
<tr>
<td>Unknown</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>0.55</td>
<td>[0.19-1.56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>0.74</td>
<td>[0.30-1.85]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy syndromes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile Myoclonic Epilepsy</td>
<td>1.00</td>
<td>[0.13-7.68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTCS</td>
<td>0.53</td>
<td>[0.17-1.61]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ref: Reference category, GTCS: Generalized tonic clonic syndrome, 95% CI = 95% Confidence interval
3.3 The time between NOE and a diagnosis of DRE

The average time between first seizure and first appointment at the SSC was 17.2 months (N=85, range 0.2-361.7 months). Without the aforementioned outliers, the average time between first seizure and first appointment at the SSC was 9 months (N=83, range 0.2-110 months). Of the 78 patients with a date for both their first SSC appointment and epilepsy diagnosis, 33 were diagnosed with epilepsy at a later follow-up date: average time being 2 months later (range 0.2-26.7 months).

In our cohort, the average time between first seizure and a diagnosis of epilepsy was 19.3 months (N=77, range 0.2-361.7 months). Eighteen patients were missing at least one of those dates. Two patients had their first seizure in the 1980s, the rest were in the recent 2000’s. Without those two outliers, the average time between first seizure and epilepsy diagnosis is only 10.5 months (N=75, range 0.2-110 months).

The majority of epilepsy patients in this cohort were diagnosed with DRE after the first year of follow-up (N=22). The average time between first seizure and the diagnosis of DRE was 27.8 months (N=18, range: 12.2-72.0 months). Out of those patients who developed DRE, one did not have a date for first seizure.
CHAPTER 4: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

4.1 Discussion

4.1.1 Drug-resistant epilepsy

Cohort studies looking at epilepsy progression or new-onset epilepsy in adult populations are limited. The present study is unique in that it followed a cohort of patients from the first diagnosis through follow-up to characterize the evolution of the condition. This is also the first study of its kind to follow an adult cohort with NOE looking specifically for the percent of epilepsy patients developing DRE. The rigorous criteria for inclusion in the study (age, seizure history, follow-up time) allowed for a unique and well-defined exploration of the course of epilepsy and various factors which may play a role in the development of epilepsy. A significant strength of this study is the source of patients. We have one of the few centers in Canada with an SSC where patients who had the first seizure in life are assessed by a neurologist, which has allowed us to develop a study cohort of carefully assessed patients for model building in the study of new-onset epilepsy.

4.1.1.1 Overall percent of DRE

The total percentage of DRE found in this adult cohort using the definition of the ILAE of NOE was 20.0%. This is lower than other cohort studies which were mainly done in epilepsy clinics. The majority of studies show rates higher than 30% of epilepsy cases who do not obtain remission via antiepileptic drug (AED) regimens.\textsuperscript{5,16,17} It is important to note that the majority of studies have been done in tertiary centers and not in single seizure clinics like ours. Studies including both older children and adults (9-93 years) indicate that 25-37% do not reach seizure freedom.\textsuperscript{20,21} Our study utilized the internationally accepted ILAE definition for DRE, whereas
the above-mentioned studies had varying criteria for defining DRE which were not necessarily validated nor were internationally accepted. Using the ILAE definition and the strict inclusion criteria increased the reliability and validity of our study.

4.1.1.2 Percentage of DRE by year of follow-up

The majority of patients to develop DRE were diagnosed in the first year of follow-up (73.7%). Of the 19 patients who met the criteria for the ILAE definition of DRE (or one of the other two definitions if censored after year 1), 14 were identified in the first year of follow-up, 1 in year 2, 1 in year 3, 0 in year 4, and 3 in year 5, making a total of 19 patients or 20% of the cohort. Three patients were not evaluated for follow-up at 12 months but were later followed up at 24 months; these cases were not found to be drug-resistant in the follow-up time of this study. Therefore, we can reasonably assume they did not significantly alter the validity of the percentage of DRE diagnosed early and throughout the follow-up period. Not all of those diagnosed in the first year remained drug-resistant by the ILAE criteria in later years of follow-up; these were solely captured by the Kwan & Brodie definition alone and did not go on to meet the criteria of any other definition (N=7).

The definition of DRE requires a certain set of criteria to be diagnosed with the condition at a given point in time. We studied patients through active follow-up processes which illustrated the dynamic nature of not only each individual’s epilepsy but the patterns of DRE presentation. When assessed year to year in follow-up for seizure frequency, medication adherence, and other comorbidities, we were able to track the progression of their condition over time. Many patients moved within categories (using either of the three definitions of drug resistance) from year to year. For example, one patient had a full 6 years of follow-up, during which they met the Kwan & Brodie definition in 4/6 years but met the ILAE definition for the first time in year 5, but not
in year 6. Potential areas of future research should include further exploration patient predictor associated with such fluctuation in the recurrence of seizures. Possible explanations of apparent intractability include AED adherence and non-epileptic seizures.

The ILAE definition utilizes 12 months as a timeline for seizure freedom and 2 years to diagnose DRE. These early periods post-epilepsy diagnosis are significant to patients in terms of overall quality of life (QOL).\textsuperscript{43} Longer periods of intractability are a negative predictor for regaining seizure remission, and are associated with worsening QOL.\textsuperscript{43,44} By evaluating this time factor and a patient’s DRE year to year, clinicians can better prognosticate their condition and QOL. Even one seizure in the previous 12 or 24 months has psychosocial consequences for a patient. In our cohort, two patients met the criteria for ILAE DRE but did not meet the same criteria at the last follow-up. Three DRE patients were still having seizures at the end of follow-up (Kwan & Brodie definition) but did not necessarily meet the ILAE criteria. Whether or not their QOL in those years differed from their criteria-meeting counterparts could be a focus of future research in a year-to-year follow-up study. A future study could assess if and how QOL changes with the fluctuating states of DRE.

4.1.1.3 Percentage of DRE by definition

Three definitions were used to evaluate DRE through the six years of follow-up. All three were validated in a previous study.\textsuperscript{38} The use of the Kwan & Brodie definition, which defines DRE as the continued occurrence of seizures, resulted in findings consistent with other studies, with a total of 31.6% DRE in the cohort.\textsuperscript{20,21} The Camfield & Camfield definition, which uses more rigorous criteria for a DRE diagnosis, resulted in a much lower rate of 10.5% DRE. In a cohort of hospital-based epilepsy patients, DRE rates were found to be 34% using Kwan & Brodie criteria, 37% using Camfield and Camfield criteria, and 33% using the ILAE definition.\textsuperscript{38}
We found no other studies evaluating the distribution of DRE by definitions amongst a cohort of adult NOE patients from referral clinics like the SSC.

Both the Kwan & Brodie and the Camfield & Camfield definitions allowed for the evaluation of DRE after the first year of follow-up, which enabled us to evaluate those patients by the ILAE definition of drug-resistance in the later years to ensure they met the internationally accepted criteria. Of the 22 patients diagnosed with DRE in the first year by either the Kwan & Brodie and the Camfield & Camfield definitions, 8 (36.4%) met the ILAE standards for DRE in the following year of follow-up, 1 (4.5%) met the ILAE in the fifth year of follow-up, 6 (27.3%) were censored after year one, and 7 (31.8%) did not ever meet ILAE standards for DRE. There were 6 patients (6.3%) in the whole cohort who met all three definition criteria at the same time at some point in their follow-up. Our cohort of adults with NOE and DRE showed very unique trajectories in terms of a drug-resistance diagnosis with some not receiving a definitive diagnosis at the end of their follow-up, despite recurring seizures.

The first year after diagnosis is a very important timeframe for evaluating the progression and prognosis of NOE, as shown by the high percentage of DRE diagnosed at the 12-month follow-up point in our study. Those patients who had only 1 year of follow-up and met both the Kwan and Brodie and Camfield & Camfield DRE diagnoses were considered DRE by ILAE criteria due to the broad encompassing nature of the two definitions together. Those who were diagnosed with DRE by the Kwan & Brodie definition alone in the first year but were censored thereafter were included in the overall percentage of DRE. These 3 patients were considered right censored before adequate evaluation of the DRE progression, but due to the evidence that seizures remained, we opted to include them in the DRE cohort. The inclusion of these three patients lowered the overall reliability of the result due to lack of confirmation of DRE by the
ILAE guidelines at year 2 and forward. This highlights the limitation in the ILAE definition as it does not seek to identify patients with DRE earlier on in their condition. This is another potential area of re-evaluation for the definition in future studies. Those patients who met the diagnosis of Kwan & Brodie DRE in the first year but did not meet the ILAE definition in the following years of follow-up, were considered not DRE for our analyses, which aimed to focus on the ILAE definition. The definition of the ILAE was created to potentially refer patients for surgical evaluation sooner than later, therefore during the first-year other definitions should be used to identify at risk patients.

4.1.1.4 Demographics of patients who developed DRE

An overview of results using cross-tabulation evaluated the basic differences between two groups of adults with NOE: those who were diagnosed with DRE in the cohort and those who were not. For demographic variables, age and sex were included.

It has been established that the risk of epilepsy is higher at the ends of the age spectrum.\textsuperscript{11-13} We assumed therefore that the risk for DRE would vary by age as well. We found in our cohort a median age of seizure onset of 33 years with a range of 12-82 years. In the 12-24-year group (N=33), 27.3% became drug-resistant, in comparison to the 25-44-year group (N=28) and 45-82-year group (N=34) with 17.9% and 14.7% drug-resistance respectively (p-value = 0.41). The two outliers in the group (age 12 and 82) did not meet the criteria for DRE at any point in the follow-up by any definition. While the statistical outcome for age is insignificant, the higher percentage of drug-resistance occurring in the younger group of NOE patients is consistent with the idea that age, and maybe more precisely time, is a key factor in the progression of epilepsy and DRE. A larger cohort with more statistical power is needed to evaluate this key variable, as findings were limited by small sample sizes in our study.
Typically more male adults are diagnosed with epilepsy, which was consistent with findings from our cohort (Table 3.1). \textsuperscript{10,11,14} Studies evaluating seizure remission and relapse have also demonstrated a higher number of males in the seizure relapse groups, which we also found in our analysis: 12 out of 49 males (24\%) versus only 7 out of 46 females (15\%) developed DRE during follow-up (p-value = 0.19).\textsuperscript{38,45} Sex should always be considered in prognosticating NOE in adults due to the known association of male sex with negative long-term outcomes in epilepsy.

\textbf{4.1.1.5 Epilepsy characteristics in patients who developed DRE}

The ILAE has created and refined the characterizing features of seizure disorders for decades. Epilepsy features such as type, seizure onset, etiology, and syndrome all play a key role in prognosticating epilepsy. Specifically, focal epilepsy type and focal seizure onset are generally more often associated with seizure relapse.\textsuperscript{46} Mesial temporal sclerosis with identified hippocampal sclerosis is more associated with seizure recurrence than other etiologies.\textsuperscript{47} In order to focus on the focal epilepsy etiologies, specifically MTS and cranial trauma, the two were combined into the term “structural etiology” and compared against all other etiologies in the chi-square analysis based on our specific patient characteristics and clinical evidence.\textsuperscript{48,49} Five patients had MTS and 4 patients had a cranial trauma etiology. Of the nine together, 4 developed DRE (44.4\%, p-value = 0.05). A larger cohort size with a more extensive exploration of the two etiologies is required to increase the validity of the combination etiology and to increase the reliability of these results. Only 1 patient had epilepsy associated with dementia, implying that these patients are possibly not referred to the SSC and are followed up by other neurologists. A future study could assess outcomes in a subset of epilepsy patients with associated neurological disorders requiring different neurological follow-up.
In the exploration of the type of epilepsy, we found that fifty-one patients were diagnosed with a focal epilepsy type, 37 with generalized, 1 with combination epilepsy, and 6 unknowns. The general interest in the association of epilepsy type with outcomes has focused on focal versus generalized epilepsy types. For statistical analysis of this risk factor, a separate variable was created to explore just focal and generalized epilepsy (N=88), those with combination or unknown epilepsy types were excluded from the analysis. There was no significant difference between those who developed DRE and those who did not in terms of epilepsy type (p-value = 0.24). In studies from tertiary centers, focal epilepsy has been identified as a risk factor for DRE, but this may differ in cohorts of new-onset epilepsy. A subsequent study with more patients will be required to explain this association, although patients with NOE may have a different clinical profile and a different evolution.

Similarly, there were 47 patients with generalized-onset seizures, 47 with focal-onset seizures, and 1 with unknown onset. The analysis focused on a variable that excluded patients with unknown seizure onset, allowing for a more reliable cross-tabulation of the variable. There was no significant difference between those who developed DRE and those who did not in terms of mode of seizure onset (p-value = 0.44).

Epilepsy syndromes were recently redefined and subsequently may be a less reliable prognostic factor when evaluating patient charts retrospectively. Nevertheless, the updated guidelines were applied to our cohort and two syndromes were identified: generalized tonic-clonic seizures alone (N=30) and juvenile myoclonic epilepsy (N=5), both of which are considered idiopathic generalized epilepsy (IGE). Twenty percent of those with JME developed DRE and 13.3% of those with GTCS alone developed DRE (p-value = 0.44).
Neuroimaging, such as CT and MRI, is key to identifying epilepsy foci, location, and often etiology as well. EEG is often an essential diagnostic tool in epilepsy. The variable for either test, abnormal or not, is utilized to explore a possible correlation between abnormal test results and epilepsy outcome. The cross-tabulation for abnormal neuroimaging identified 26 patients, 5 of which developed DRE in the follow-up (19.2%, p-value = 0.94). Seventy-five patients had an abnormal EEG, 15 of which developed DRE (20.0%, p-value = 0.61). The higher number of patients with an abnormal EEG may be related to the fact that EEG is a routine test at the SSC where every patient receives at least 1 standard 20-minute EEG throughout follow-up. Ambulatory EEG’s and telemetry EEG’s are included in the variable for “abnormal EEG” as we required any one EEG with abnormal results to definitively characterize a given patient’s condition. MRI is not standard testing for NOE patients but is ordered when clinically relevant. The results for the cross-tabulation for abnormal test results indicate no significant difference between the two groups tested at any given point in time.

4.2 Evaluating the development of DRE with key independent variables

4.2.1 Bivariate analysis

The outcome variable DRE is a dichotomous dependent variable that we evaluated over the full follow-up period. Given the time-to-outcome focus, a proportional hazards analysis was the most appropriate statistical analysis. By focusing on the time that it takes for DRE to develop in association with risk factors, the survival time of patients with different epilepsy characteristics can guide prognosis and clinical treatment in the future.

Similarly to the cross-tabulation evaluation above, 8 risk factors were assessed for their association with the development of DRE over time. A p-value of 0.25 was set for creating a
multivariate model. Although this may be considered a liberal set-point for further analysis of risk factors, it allowed for the assessment of clinically significant variables in a small cohort with low statistical power. By doing so, it will guide our future studies with a larger cohort. From this bivariate analysis, 3 variables could be further assessed in a multivariate model: age of onset, sex, and etiology.

The age category for 12-24 years for epilepsy onset had a hazard ratio of 2.02 (CI: 0.68-6.06, p-value=0.21) in comparison to the reference group (45-82 years). While this is not a statistically significant outcome for age, it does not rule out the importance of age at seizure onset in considering the prognosis of NOE patients. Patients of any age are at risk for developing DRE, but studies in adults indicating younger age at onset is a risk factor in NOE progression to DRE have not been published to our knowledge.

Sex was associated with a hazard ratio of 1.75 (CI: 0.69-4.45, p-value 0.24). While a non-significant result, it does not rule out the contribution that sex may have on the prognosis of epilepsy. To our knowledge, sex has not been identified by others as a risk factor in the development of DRE in adults.

Etiology is a clinically significant risk factor to establish when considering the prognosis of NOE, and our bivariate analysis indicated that it was a necessary variable to include in the multivariate analysis. While the overall category of etiology made the criteria of p-value <0.25 to be included in the multivariate analysis, the individual categories were not statistically significant: MTS (HR: 2.57, CI: 0.71-9.34), cranial trauma (HR: 0.73, CI: 0.09-6.06), masses (HR: 0.50, CI: 0.07-3.86), and cortical dysplasia (HR: 1.56, CI: 0.19-13.0). Each had confidence intervals including 1 and p-values >0.05.
Prior studies have explored the clinical predictors of seizure relapse and remission in a broader group of epilepsy patients via logistic and cox regression analyses.\textsuperscript{44,45} Common predictors between those studies and ours include younger age at epilepsy onset and etiology. In particular, cranial trauma as the cause of epilepsy was shown to be a negative predictor of seizure remission in these studies. The etiological category highlighted in our cohort was MTS, which can commonly be caused by cranial trauma.\textsuperscript{48} When cranial trauma and MTS were grouped (as seen in Table 3.4 as “structural lesion”) the bivariate Cox regression analysis revealed a p-value $>0.25$ and was thereby not evaluated further. Instead, the individual etiologies were evaluated and included in Table 3.5. The relationship between MTS and cranial trauma, with DRE in a cohort of NOE in adults, should be a focus of future research in a cohort with a larger sample size. Regardless, our results were concordant with previous studies.

Both GTCS alone and JME are considered idiopathic generalized epilepsy (IGE). JME stereotypically appears during early adolescence, however, some cases can start later in life. Studies indicate the key features of JME have a peak age-related onset between 14 and 15 years of age.\textsuperscript{51} With these cases, either the first known myoclonic jerk or first seizure was used for the “age of onset” variable. We recognize that patients with JME likely had myoclonic jerks before a well-defined seizure and epilepsy diagnosis. Patients with JME are often diagnosed late and retrospectively.\textsuperscript{52} Because the diagnosis of epilepsy was made in adult years for our patients, patients with JME were included in the study, although the category did not yield low enough p-values to be evaluated past the bivariate analysis.

Neuroimaging is of interest because while studies have indicated that focal epilepsy is more difficult to control than other epilepsy types, there are more specific studies which indicate that only temporal lobe epilepsy with evidence of hippocampal sclerosis or cortical dysplasia...
result in increased risk of developing DRE.\textsuperscript{46,52,53} Such etiologies would more often be identified in imaging, thereby making a diagnosis of focal epilepsy more specific in terms of the correlation with DRE outcomes. Specific correlations between imaging findings, etiologies, and DRE have been deferred to a later time.

A note on non-parametric statistical models: the statistical analyses chosen for our study were non-parametric, meaning they could be applied without any previous knowledge about the cohort nor without any basic assumptions needing to be met.\textsuperscript{54} The distribution of participant parameters is arbitrary. The positive aspects of utilizing non-parametric models include flexibility in application to a non-random sample, a small cohort, ordinal or nominal data, and limitation of effects from outliers.\textsuperscript{54} However, non-parametric models consequently have lower statistical power than parametric models.\textsuperscript{54}

4.2.1.1 Survival curves: Kaplan Meier curves

The survival data for this cohort was right-censored. At the point the study ended, the outcomes of the patients who did not develop the event (DRE) were either still being followed, lost to follow-up, or had died. The outcome of their condition regarding the development of DRE is unknown, so they were censored for survival analysis. This allowed us to include the contributions of all patients until they left the analysis, or the study ended, regardless of their undetermined outcome. Because we assume the censoring occurred evenly throughout the follow-up period, we were able to assume random censoring, which bolstered the validity of the censorship assumption in a cohort of this nature.\textsuperscript{50}

To account for the unknown outcomes throughout follow-up, the rate of DRE was calculated at multiple points in the follow-up for all those in the study and not yet censored.\textsuperscript{50} This is illustrated on a Kaplan-Meier survival curve: the probability of survival (or percent
survival) versus time. In our plots, the outcome was evaluated at the end of each year of follow-up, measured in months. Figures 3.2-3.9 illustrate the survival curves (predicted & observed) for each of the eight risk facts over time with the outcome being the development of drug-resistance. The predicted and observed curves were in close proximity for all independent variables, suggesting the PH assumptions were met and the hazard for an individual with those risk factors were equal over time.

4.2.1.2 Survival curves: Log-log plots

Another method of assessing the PH assumptions was to graph the log(-log(survival)) versus the log of survival time, also called a log-log plot. The log-log survival curves should be parallel between the categories of the independent variables over the length of follow-up. Log-log plots of the independent variables analyzed in the bivariate Cox regression revealed parallel curves between the categories of each independent variable. Non-parallelism recurred for several variables at the beginning and end of each graph, where observations were fewer. Notable areas of non-parallelism were seen in the independent variable etiology, where MTS and cortical dysplasia crossed near the center of the survival curve. The crossing of categories indicates that the hazards for those etiologies were not proportional over time.

While the graphical approaches were a subjective assessment of the PH assumptions, they were useful in identifying specific violations with the variables in the sample of patients, even if the objective test results were non-significant.

4.2.1.3 Goodness of fit test

The third way we were able to assess the PH assumptions for the independent variables was using the Goodness of fit (GOF) test. The test applies Schoenfeld residuals to each predictor
in the model and for every participant who has an event (DRE). It produces p-values to indicate an objective assessment of the PH assumptions. If the variable meets the PH assumptions, then the Schoenfeld residual for that variable will not be associated with survival time. In the case of our bivariate analysis, each analysis had one Schoenfeld residual applied and tested. Of the 8 risk factors, 5 had p-values >0.05 (age: 0.62, sex: 0.73, abnormal EEG: 0.63, abnormal imaging: 0.13, etiology: 0.15), suggesting that they meet the PH assumptions. The variables epilepsy type (p-value: 0.004), seizure type (p-value: 0.01), and epilepsy syndromes (p-value: 0.001) produced did not meet the PH assumptions.

Both the subjective and objective methods of assessing the PH assumption are recommended for evaluating the validity of the independent variables in hazard analysis for DRE.40

4.2.2 Multivariate analysis

Our analysis found no statistically significant predictors for the final model. The risk factors age of onset, sex, and etiology were included in the initial model based on p-values obtained from the bivariate analyses. A backward stepwise model building strategy was conducted. Sex and etiology were both eliminated based on p-values produced by the LRT (Equation 1), leaving no multivariable model with significant predictors. The LRT compared the full model to a reduced model for each of the risk factors, producing a p-value and confidence intervals indicating their statistical contribution to developing DRE throughout follow-up. Similarly, the variables age and sex were assessed as confounders based on prior literature (Equation 2). Both risk factors produced values <10%, and therefore were not significant confounders in our final model. Age and etiology were assessed as an interaction term (age*etiology) which did not produce statistically significant p-values and therefore was not
included in the model. Collectively, age, sex, and etiology independently together had a p-value of 0.47.

More specifically in the multivariate model, the ages 12-24 years at onset had an HR of 1.68 (CI: 0.53-5.36) and 25-44 years at onset had an HR of 0.92 (CI: 0.22-3.91), when in conjunction with sex and etiology. The confidence intervals include 1, further indicating a lack of statistical significance. We cannot interpret the age of seizure onset as having any significant contribution to the development of DRE in this population when in a model with sex and etiology. Similarly, being of male gender (HR: 1.85, CI: 0.65-5.29) lacked a supporting CI and therefore cannot be interpreted as statistically significant in the development of DRE in the multivariate model. The undifferentiated category etiology overall had an HR of 1.03 (CI: 0.91-1.16), bordering on a significant association. However, the differentiated categories MTS (HR: 2.57, CI: 0.70-9.57), cranial trauma (HR:0.73, CI: 0.07-7.78), masses (HR: 0.50, CI: 0.06-4.06), and cortical dysplasia (HR: 1.56, CI: 0.24-24.43) did not add anything to the risk of DRE development in the full model.

The addition of individual variables to the model did not explain any new variation in DRE development. The three risk factors may be related and therefore their individual estimated hazard decreased to non-significance. It is possible they overlapped in variance and therefore collectively did not show a combined contribution to the outcome development. If the sample were larger and each risk factor had a greater scope of assessment of both DRE patients and non-DRE patients in the time course of DRE development, the outcomes might potentially show more statistically interpretable outcomes. This is a goal for the future of this project.
4.3 The time between NOE and a diagnosis of DRE

Descriptive statistics were utilized to evaluate the average time between stages of the condition: onset, diagnosis, and DRE development. In this cohort of 95 adult patients with NOE, there was an average time of 19.3 months (N=77, range 0.2-361.7 months) between first seizure and a formal diagnosis of epilepsy. The average time between the first seizure and first appointment at the SSC was 17.2 months (N=85, range 0.2-361.7 month). The average time between the first seizure and the diagnosis of DRE was 27.8 months (N=18, range: 12.2-72.0 months).

The focus of this descriptive analysis was the time elapsed between the onset of seizures and the development, or diagnosis, of DRE. The treatment history and duration of epilepsy are established risk factors for relapse over time and therefore are necessary points of observation in a follow-up study of this nature.\textsuperscript{56} Two prior studies, a pediatric and an all-ages prospective cohort study, indicated the latency period between onset of seizures and failure of the second AED was 9.1 and 9.7 years, respectively.\textsuperscript{57,58} The vast majority of patients in all ages study were <18 years of age, which is an important point to consider when applying such timelines to an adult cohort. The treatment process and timeline for adults with NOE are clinically different. As it is, the wait time for epilepsy surgery for adults in Saskatchewan is almost 20 years, similar to other centers which found 22.1 years.\textsuperscript{58,59} Given that the definition of DRE utilizes a timeline of 2 years, there should be a much more rapid referral to epilepsy surgery in our province. Having a better clinical understanding of NOE at the start and the prognosis of an individual’s condition, specifically those that are focal epilepsies, could theoretically speed up the course of management and time waiting for potentially curative surgery.
According to Kleinbaum & Klein (2012), using descriptive statistics is a suitable method to determine the average survival time in a cohort. However, a notable flaw is the fact that such methods do not compare the groups at different points in follow-up, just simply an overall comparison. The results of this average then must be taken with that in mind when evaluating the timeline of this condition. As previously discussed, NOE is a dynamic condition process that fluctuates in drug-responsiveness according to several intrinsic and extrinsic variables.

4.4 Strengths and limitations of the study

This is the only study of its kind and is important research in terms of mapping the progression of NOE in an adult-specific cohort. Typically, epilepsy is recognized and diagnosed in children primarily and the research historically has focused on children. By identifying and following adults from the first seizure through the referral program set up at the SSC in Saskatchewan, we have the unique opportunity to diagnose, treat, and follow-up individual patients over their lifetime, but also have the ability to gain greater understanding of general condition progression in the cohort.

The main strength of this study is the use of different definitions to assess DRE as well as also the assessment by year. This has contributed to more accurate estimates of DRE in patients with NOE. Currently, there are mainly pediatric studies in epilepsy, so the information provided in this study will be useful for clinicians and researchers who mainly target adult patients with epilepsy. Also, the shorter follow-up time reduced the likelihood that changes in efficacy of the available AEDs affected the changes seen over the years.

Over 6 years there were many patients diagnosed with epilepsy in their adult years, but not many met the criteria of at least 1-year follow-up, no history of seizures, or no suspect substance-withdrawal seizures. Because of the unique and specific criteria used, only 95 were
eligible for inclusion in the timeframe chosen. Consequently, our statistical power as a cohort was low. We hypothesize that with a few more years passed now, we can increase the cohort size and by extension, the statistical power.

Further affecting significant results was the strictness with statistical methods. While a significant variable was identified in the cross-tabulation study, it did not remain so when Cox regression analysis was applied; therefore, we did not find any significant results.

P-values are driven by sample size. A concern with a quantitative testing approach (i.e. the GOF) is that the null hypothesis can never be proven. At most, we can say there is not enough evidence to reject the null. Furthermore, any gross violation of a null hypothesis may not be significant if the sample size is small, as is the case with our cohort.

As it stands now, the cohort involves all adult patients referred and seen at the SSC who met NOE criteria. This has limitations because of reduced patient inclusion from the far northern and southern aspects of the province where accessibility was a significant barrier. The SSC also would not have seen adults with NOE who were followed by a family physician or neurologist without referral to the SSC. This is less common though given the new standards for a referral to the SSC in the province (referral of all suspected first seizures in adults to the SSC). However, we cannot reliably calculate what percentage of the Saskatchewan population we have captured with existing resources.

The definitions for NOE and NDE lack a time variable, in that the time between first and second seizures is not accounted for when considering a diagnosis of epilepsy. This makes the assessment of the condition status less reliable when looking at the time to DRE onset.

In terms of the patient cohort, the SSC patient screening tools at present do not ask for ethnicity, therefore it is generally not included in patient charts. For this reason, we chose not to
include ethnicity, or indigenous ancestry, as a risk factor in this study. This is a significant limitation given recent publications in Canada showing that indigenous persons are at twice the risk for developing epilepsy. It would then be reasonable to assume that it should be included as a risk factor for the progression of the condition as well, along with other ethnicities.

4.5 Implications

This study has important implications for the guidance and treatment of adult patients with NOE. In particular, clinicians will be able to better predict and counsel patients about their unique condition in the future with the extension of this study. Currently, our study does not meet enough criteria to determine causality from an epidemiological perspective, in particular, the criteria of strength of association. Although we did not find a lot of risk factors for developing DRE in patients with NOE, the analysis by years and using different definitions used in this study made this project a valuable source of information for clinicians, epilepsy associations and key observations about the use of the definition of DRE by the ILAE.

4.6 Conclusion

The purpose of this study was to characterize the development of drug-resistance in a purely adult cohort with NOE diagnosis from the Single Seizure Clinic in Saskatchewan, Canada. The prospective study looked at 95 patients from 1-6 years of possible follow-up between 2011-2017. The data collected allowed the collection of risk factor data and the subsequent analysis of this data to explore possible relationships to the development of DRE over time through a time-dependent Cox-regression analysis.

Although the development of DRE has been described in studies around the world, this is the first study of its kind from an SSC looking solely at an adult cohort with NOE. This type of
secular analysis is very useful to the characterization of DRE in patients with NOE. Overall the rates of DRE are lower than the ones seen in studies done in hospitals or epilepsy programs.

We utilized three of the most widely accepted and validated definitions to tailor our analysis to the first-year post-diagnosis and onward. This was necessary as the internationally accepted definition for DRE does not characterize the condition until the second-year post-diagnosis. All three definitions characterize the condition on a spectrum, from broadly categorizing seizure quantity to more specific details about treatment and seizure frequency. This strengthened the overall analysis of our cohort and their condition course trajectories. We discussed the necessity of characterizing NOE early on in terms of outcomes and QOL, which guided the goals of this study to focus on the first year and afterward.

The results of this study did not identify specific risk factors, likely due to the specific inclusion criteria leading to small sample size. Patterns been hypothesized in terms of at-risk etiologies, which could be used as starting points in an expanded adult-only NOE project later on. The information gathered from this study is of value to clinicians and clinical researchers in terms of how to best approach and evaluate adult patients with NOE.

Identifying patients at risk for DRE early on in their condition is vital to decreasing wait-times for possibly curative epilepsy surgery in Saskatchewan. Given that this healthcare system has a substantial wait-time crisis on its hands, there is an important need to focus research such as this on NOE, preventing long-term consequences of surgical waitlists, and decreasing overall burden on the healthcare system long-term.
References


