"Are Deaths Due To Epilepsy Preventable?"

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Abstract

Recent studies on epilepsy mortality have shown that deaths due to epilepsy would have been preventable in the majority of cases. Over the years, research on epilepsy has prioritized one of the major causes of death, which is Sudden Unexpected Death in Epilepsy (SUDEP).

This study pursues a holistic approach and classifies epilepsy-related deaths into direct, indirect, undetermined, and unrelated causes of mortality. It uses a meta-analysis approach and data from eight articles published from 2008-2018. The Standardized Mortality Rate (SMR) is used as the independent variable and the study compares it with rural and urban population data along with the direct and indirect causes of deaths in people with epilepsy. The findings of this study have shown that the standard mortality rates (SMR) in both rural and urban populations are almost the same. Furthermore, the majority of deaths occurring in urban areas are due to unrelated causes, which are unlikely to be preventable, while deaths happening in rural areas, due to indirect causes, are more likely to be preventable. This study suggests that there should be firm guidelines on classifying different kinds of deaths.

Introduction

What is Epilepsy?

The term 'epilepsy' is defined as a chronic non-communicable brain disease [1]. A person with epilepsy will usually have recurring seizures due to the sudden outburst of electrical activity in the brain, leading to disruption of the brain. It has been noted that deaths caused by epilepsy give rise to the global burden of mortality in general. Most literature on epilepsy mortality focuses on one specific form of death, which is called the Sudden Expected Death in Epilepsy (SUDEP). SUDEP is defined as a form of death, which is non-traumatic and non-drowning in nature. Consequently, research has neglected other causes of death and focuses more on SUDEP, which is only the second leading cause of death among the epilepsy population. These deaths among people with epilepsy (PWE) are occurring prematurely. The term 'premature death' in any given population is defined as the heightened risk of death for a person due to a specific cause when compared to the general population. Moreover, the risk of premature mortality in those with epilepsy is eleven times more than the general population [2]. This has further given rise to an analytical approach where researchers have specifically looked only into SUDEP and not into other types of death that are possible due to other risk factors. This particular topic on epilepsy mortality was chosen because most of the epilepsy organisations around the world provide information or emphasize more on SUDEP rather than discussing every form of death that is possible for a person with epilepsy. The preference for this topic is also because of the personal resonance that led to embarking on research and adding to the body of literature in epilepsy mortality research. The overall aim of this study is to combine mortality data from 2008-2018 and evaluate and classify the major causes of death by examining if they could be preventable.

There are several causes known to be behind premature mortality in epilepsy. Most literature lacks firm guidelines as to specify different causes of death in epilepsy. This study proposes a split classification of epilepsy-related deaths (ERD) into direct, indirect causes, unrelated and undetermined causes. The

direct causes of death include deaths as a result of status epilepticus and SUDEP, which will be discussed later. The second category proposed are the indirect deaths and is basically deaths due to accidents in the form of injury, burns or accidents that happen when PWE are unconscious while having a seizure. The third category is undetermined or unrelated causes which include other possible medical condition together with epilepsy make it challenging to find the possibility of death. Even though it is known that direct causes contribute to very few numbers of deaths among PWE, some studies over the years have given more attention to direct causes and specifically to SUDEP. Over the years, researchers have been trying to study the cause behind SUDEP and how it could be prevented. It is estimated that there are about 1,000 deaths annually occurring due to epilepsy in the UK [3] and the number of deaths due to SUDEP is about 600 people annually. Research over the years has confirmed that people with epilepsy are more likely to have a premature death and die before their mid-fifties. The last few years have seen a drastic increase in these kinds of epilepsy-related deaths. The exact causes behind these deaths, in general, are an ongoing challenge for researchers. With the rise in epilepsy deaths, the risk factors have also doubled over the course of time, with the major challenge overall being making an effort to minimize these deaths. As a result, researchers have prioritized this concern over other epilepsy 'hot' topics, because some believe these deaths are preventable. Furthermore, SUDEP is currently a 'trending' topic in epilepsy research, which has made other risk factors less of a priority. This study addresses this issue by conducting a meta-analysis, and comparing the mortality rates of some of the major epilepsy-related deaths, which are direct, indirect, unrelated and undetermined. The findings for this study will present a fresh perspective on the risk factors that should be prioritized, and will critically evaluate whether these causes are preventable or not.

Literature Review

Prevalence of Epilepsy

According to the Institute of Medicine, there are about 65 million people affected by epilepsy worldwide [4]. On the other hand, deaths due to epilepsy are higher than the data used suggests. Furthermore, premature deaths are commonly found in this population. Co-morbidities and aetiology are the known factors behind these premature deaths. According to Salema and Jackson, there has been a spike in mortality rate by 70% from the year 2011 to 2014.

Epilepsy Diagnosis and Intervention

Diagnosing epilepsy is one of the most challenging issues due to several seizure types, and a wide range of symptoms a person might be experiencing

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with its aetiology. Intervention plays a key role beyond diagnosing epilepsy. Moreover, epilepsy is a kind of chronic illness that has to do more than localising a seizure or lesion in the brain. There is not a standard procedure or protocol for diagnosing epilepsy. Usually, a treatment approach in epilepsy includes an intervention that has an assessment to find out the kind of seizure a person might have and based on that a person is prescribed medication that is usually anti-epilepsy drugs (AEDs). It is estimated that for about 30% of PWE AEDs might not be an option and for these people either surgery or other forms of treatment might work out. In spite of these statistics for those whose seizures are under the control of AEDs and others who do not really affect the risk of mortality due to the various causes. However, for some people after surgery they might become seizure-free and without taking any medications. The risk of death among all those affected with epilepsy remains the same except for those who are seizure-free without any medications are not affected. Research still struggles to find out what causes epilepsy [5]. This further explains what makes epilepsy mortality challenging to address. This study bridges the gap by examining the different deaths and making recommendations to the treatment strategy that will be discussed at the end.

The Possible Significance of Epilepsy Mortality Research

Certain studies on psychiatric comorbidity in epilepsy have shown that eliminating premature mortality from indirect causes of death should be paid more attention. According to Fazel, Wolf, Langstrom, Newton & Lichtenstein, the role of comorbid in deaths with PWE is unknown [6]. Their study had Sweden born participants from 1954-2009 with inpatient and outpatient diagnosis of epilepsy. In their study, there were about 6,155 deaths out of 6, 60,869 where the median age was 34.5. Within the whole sample, there were about 972 deaths due to indirect causes such as non-vehicle accidents and suicide. Overall, the study pointed out how careers and people with epilepsy were not made aware of various risk factors that could lead to death. Another of the major challenge when it comes to research in epilepsy mortality is the lack of systematic classification in the different types of deaths that could happen for a person with epilepsy. This has further caused complications in the data collection process in epilepsy mortality research and this study precisely differentiates the various causes of death into three for simplification and in order to study the relation of the causes and the death rate.

Mortality Data

Literature suggests that understanding mortality data helps to know the problems of health and disease in a population [7]. Similarly, knowing the root cause behind the issue will help clinicians and researchers to come up with an effective diagnosis. In the UK, epilepsy-related deaths are often underestimated. It is estimated that there are over 1000 epilepsy-related deaths in the UK [8]. About 50% of these deaths are caused due to SUDEP, while the remaining 50% happen due to accidents, drowning, status epilepticus, and suicide. Subsequent studies on epilepsy-related deaths have shown that risk factors help to learn about mortality. For instance, an in-hospital study on 12365 patients with status epileptics out of which 117 died of cerebral palsy, pneumonia, and respiratory condition showed that symptoms, seizure frequency and medications help to predict mortality [9].

Mortality Rate

Mortality rate plays a significant role in research irrespective of the field of interest. Research in mortality has different terminologies to have a better understanding of scientific relations in the research. Some of the common terms that will be used throughout this study include Standardised Mortality Ratio (SMR) and Proportionate Mortality Ratio (PMR). The term Standard Mortality Ratio (SMR) is defined as the standardised mortality ratio. This ratio is yielded by dividing the observed deaths to expected deaths. This ratio is dependent on age, gender, and population. To have a better understanding in a real-world scenario it is said that if the SMR is greater than 1.0 then the population must be having a higher death rate. SMR helps to understand more about the death patterns in a population in terms of finding the leading cause for a particular problem. For this study, the role of SMR as an independent variable is to find whether the different causes of

epilepsy have an effect in rural and urban populations. Beyond the ratio, the SMR helps to learn about different predictors related to mortality and this could be age, gender and other underlying factors contributing to that death rate. SMR also helps to study the underlying cause in a health condition. For example, in a clinical cohort study on epilepsy in India, it was found out that the SMR varied from 2.58 to 7.6. When conducting mortality research it is essential to know that a SMR < 1 is better than > 1 [10]. Additionally, it helps to explore and learn more about the aetiology, follow up conditions, physiological and environmental factors as well as demographic factors [11]. While the term 'PMR' is defined as the absolute number of deaths in a given group of people due to a particular health condition. In other words, it helps to learn more about the cause-specific risks in a population. Therefore, the SMR gives a researcher powerful insights about learning underlying issues in a health condition from different aspects and PMR is an essential tool to explore the significance of cause-specific risks in a given sample. This study will elaborate which cause affects the majority of these death rates and then examine if there is any variation among these causes in two different socio-economic populations.

Mortality in Epilepsy

Considering epilepsy as a long term chronic illness, it is more likely for a person to be at risk for death. Most importantly people with epilepsy are prone to having a premature death as a result of misdiagnosis, tenure of treatment and other related problems. Furthermore, one thing common in all of the risk factors for epilepsy-related deaths is in the aetiology. When looking into general studies on epilepsy mortality, it is very interesting to find that most deaths are relevant to the young population because of aetiology. According to Shackleton, Westendorp, Kasteleijn-Nolst Trenite, Vandenbroucke, this 40 year follow-up study on a dutch cohort surveyed 38665 patients in which 404 had died during the follow-up [12]. The result demonstrated that the mortality rate was higher in men than in women and the age range in which most deaths occurred was below 20 years of age. The study majorly pointed out that the deaths were mostly an outcome of direct causes of death. However, there are mortality studies that have shown that indirect causes are certainly responsible for these deaths. For instance, a mortality study in rural china among people with epilepsy has shown that premature mortality is 3-4 times higher when compared to the general population. Most of these indirect causes include injury, stroke, neoplasm, myocardial infarction [13]. Significantly, it has been observed that most of the deaths happening prematurely in a hospital setting had a direct correlation with psychiatric comorbidity. The deaths under this category fall under undetermined causes. Despite different causes in these studies, premature mortality was common in all of them and people with epilepsy are more prone to death due to their condition. While the research could defer based on the geographical location or income level, research in the UK holds something different. Literature comparing rural and urban areas on epilepsy mortality shows a lack of data or research done in developing countries. According to Ridsdale, Charlton, Ashworth, Richardson and Gulliford, mortality risk factors related to epilepsy deaths are not well understood. In their study, mortality data from 1993-2007 showed an increase in mortality rate from 9 deaths in every 1000 people in 1993 to 12 deaths per 1000 people in 2007 [14]. The study purported that deaths were an outcome of indirect causes. Comparison studies on both direct and indirect causes of death have shown interesting findings. For example, according to Kwon, Liu, Quan, Thao, Wiebe and Jette, their study on 10240 PWE and the control group of 40960 people who did not have epilepsy revealed that PWE is more likely to die from assaults then suicide. Their study looked into indirect causes of death specifically motor vehicle accidents, suicide and assaults in PWE population. This study showed that stricter laws might be helpful in preventing these deaths [15].

In brief, research over the years have concluded that the major gaps currently are observed in terms of prevention measures, consistency of definition especially when defining direct, indirect and undetermined causes [16]. Besides these gaps, research has become clearer that these deaths could be prevented. This study will address these gaps by comparing the various types of deaths taking place in different socioeconomic countries around the world.

Significance of Location in Epilepsy Mortality

Location is an interesting contributing factor to epilepsy mortality. It works as an interesting factor for comparing samples and learning about aetiology. This study will be comparing SMR in rural and urban areas. Even though the data set included information for middle-income areas, there was no significant outcome. An urban area in this context is defined as a region that is surrounding a city, which is very developed, and has non-agricultural jobs [17]. The second type of population that will be discussed is a rural area. According to Rutledge et al., a rural area is defined as a type of settlement that has low population density and most of the area is not developed. Furthermore, it is expected that rural areas would have a higher SMR because they would not have proper access to treatment, whereas urban areas would do a much better job and thereby have a lower mortality rate [17]. However, there has been limited research showing that there are not any significant drastic changes in these statistics. This makes it a bit challenging to know whether the diagnosis or treatment is effective or could be made better. Previous research has shown that mortality rate and death could vary based on location and income level of a place. According to Bowman, Aitkan and Sharp, people with epilepsy are more likely to die in hospital then they would die at home. Another study in premature mortality of epilepsy was compared to low and middle-income countries [18]. The estimated mortality in this study was 19.8 per 1000 people. This study showed that premature mortality was higher in high-income areas and low-income areas had higher mortality, especially in rural areas. In a systematic review which focused on the global disparities in epilepsy treatment found that there is a 75% gap in low-income area and 50% gap in lower-middle and upper-middle areas [19]. Significant research on mortality rates of epilepsy has shown that the causes of death could vary due to the location. For example, burns are a leading cause of death in South Africa. According to Scheven, Barker and Govindasamy, there were about 20.5% of deaths occurred in those with epilepsy due to burns. The cause of death is indirect in this context and the study reiterated how practising community health education programs would be beneficial to address this challenge [20]. On the contrary, there could be other changes that could be observed like the treatment gap. Some research has shown that there is absolutely no significant trend in treatment gap over a course of time [19]. Some studies have reported that despite having a similar rate of SMR in low income and high-income areas, the death rate does not get impacted. For instance, a longitudinal study on 52,377 PWE out of which only 20 died showed a SMR of 2.58. This study showed no significant difference between a slum and non-slum dwellers [21]. In other words, there were no changes in the number of deaths between low and high-income country. Thus, the level of effective treatment and mortality could be different based on the location and income of a place. Even till this day, all of the risk factors for epilepsy that were discussed previously are considered controversial mainly because of different factors. This study addresses the challenge by examining differences in direct, indirect, unrelated and undetermined causes of death. All of these three causes include incidents such as suicide, SUDEP, status epileptics, burns, accidents, assaults, drowning which has been defined and categorized later to have a better understanding. By comparing the two types of socio-economic countries, this study will help address if direct causes such as SUDEP has been overemphasized over the literature. Therefore, this paper will evaluate each of the risk factors and will provide suggestions in order to intervene in these risks during the diagnosis.

Types of Deaths

Understanding deaths in epilepsy population could be complex due to several risk factors and different types of death. To have a better understanding of epilepsy-related deaths, the risk factors are divided into direct, indirect, unrelated and undetermined causes. Direct causes are defined as when death happens due to an outcome of a seizure [22]. These causes include the latest terminologies in epilepsy research such as status epileptics and SUDEP. The indirect cause of death is when a person dies during their seizure and these include mainly unforeseen accidents. These could be in the form of burns, falls, drowning or reaction to antiepileptic drugs (AEDs) [22] as well. On the other hand, there are deaths as a result of unrelated causes of epilepsy or they might not be ascertained [22]. Some studies

have shown despite cutting edge research in epilepsy, one of the major challenges most literature cites that deaths due to the direct consequence of epilepsy are more common than the other causes. As a result, the priority of research in epilepsy-related deaths has taken a different approach by leading researchers to address the challenges of SUDEP.

Among all the forms of death due to direct, indirect, and undermined or unrelated causes, it is known that SUDEP, status epilepticus, and suicide have higher prevalence rate. The exact reason for epilepsy mortality is unknown up to this day. Furthermore, the leading drawback in this topic is that research tends to address this issue by having a biological approach. A lack of systematic research on epilepsy mortality has given rise to not having a clear cut procedure of conducting research on mortality and studying about the various risk factors, which have further caused researchers to approach the only SUDEP in every different perspective as possible. In addition to that, recent research on epilepsy-related deaths focuses on making public aware of the risk factors of SUDEP rather than general risk factors for epilepsy-related deaths. This study provides a solution by analysing common types of death possible for a PWE. The study discusses each type of death that is commonly possible and proposes a unique approach to prevent these deaths.

Methodology

Outline of the Data for the Meta-Analysis

For this study, there were 15,594 articles that showed up on the search results for the three databases that include ScienceDirect, Scopus and Medline. The terms 'SUDEP', status epilepticus, epilepsy mortality, deaths due to epilepsy were used in the search terms. During the streamlined process for the articles, we included data such as SMR, types of death (death from direct causes like status epilepticus or SUDEP or deaths from indirect causes like burns, accidents, assaults) socio-economic status of the country i.e. whether rural or urban area population. Studies chosen for this study were conducted in Bolivia, England, India, Kenya, China and Brazil. In the initial stage of the literature search, we had to refine and select studies from 15,594 articles from these three databases. This was done by reviewing articles and abstracts that met the criteria for this study discussed in the next section. Studies that had incomplete data were excluded from the meta-analysis.

Inclusion Criteria for the Study

The data for this study also included information like the number of deaths, year and some studies also had PMR rate which was excluded. The criteria for this meta-analysis included studies from 2008 to 2018.
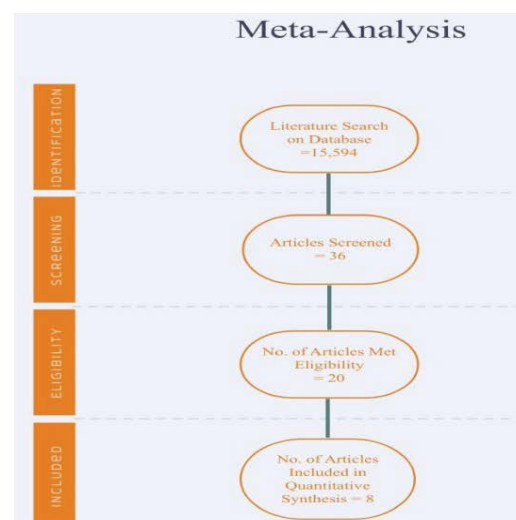

Figure 1. Flowchart for the Criteria of the Meta-Analysis.

Criteria for the Meta-Analysis

The studies that were included for this meta-analysis made sure it focused on the general population rather than being specific like pediatric, older age group or vice versa. The studies specifically looked into articles that had a proper classification of Epilepsy-Related Deaths (ERD). In other words, the studies that classified deaths only as indirect, direct causes, unrelated and undetermined causes. Despite the difference between unrelated and undetermined causes of death in epilepsy, this study categorised unrelated and undetermined causes of death as one because the major purpose was to learn about direct and indirect causes of death. Moreover, the other two causes (unrelated and undetermined) are the causes that still need to be addressed in the future. All the studies for this study were either population-based or clinical cohorts. It was also made sure that all the articles for this study approached epilepsy in a general way rather than focusing on a specific type of seizure. There was data available on unrelated or undetermined causes of death that was excluded as we are specifically looking into direct and indirect relationships in different levels of income. The different forms of death were defined and other medical terms like SUDEP, status epilepticus and SMR using the standard definition from the International League Against Epilepsy (ILAE). Mortality variable i.e. SMR for the study was collected by recording the SMR ratio. This was obtained by dividing the total number of deaths by the expected number of deaths in that particular region.

Ethics and Dissemination

No ethical approval was required since data from previous studies in which informed consent was obtained by the primary investigators will be retrieved and analysed. This Dissertation did not involve human participants. Ethics was agreed with the author's supervisor, Chris Barker.

Initial Analysis of the Meta-Analysis Data

After the initial extraction of data, the data were categorised into the urban and rural population and different variables were compared. The comparison variables in both the population type were SMR, number of deaths and different causes of death. The overall data from these studies gave an idea about the different causes of death and compared mortality based on different economic status, mortality rate and a number of deaths, which could be found in Table 1 below.

The data also provides a brief knowledge about the priorities for future research which will be discussed later.

From this study, we conducted a classical meta-analysis and obtained the results. The analysis included data from 8 articles that met the ultimate criteria and represented a rural and urban area population. These studies were within 10-year span chosen from 2008-2018. The study examined the effect of direct causes of death in SMR which was significant. We used a fixed-effect model and a statistical test called Omnibus test of the model coefficient for the p-value, which is mentioned below in Table 2.

It could be inferred from the fixed-effect model that the Omnibus test of the model coefficient was significant for our research. Furthermore, the wald test or the chi-squared test found that the p-value was significant, which confirmed that direct causes had a significant effect on the overall SMR. The funnel plot for this study demonstrated that there was no significant publication bias because the distance from the central axis to the plots were very close to each other. The descriptive statistics for the study include the total number of deaths in this population, which was 631 and the sample size of this whole study was 8,413. As per the descriptives below, the mean SMR was 3.83 whereas the minimum and maximum value was 1.0 and 7.1 respectively. From the whole study sample, 39.30% deaths were due to unrelated causes, 26.7% deaths due to indirect causes, 21.87% deaths due to direct causes and 12.04% of deaths due to undetermined causes. When we looked into the more specifically by comparing rural and urban population, the analysis revealed that the majority of the deaths in the whole study sample occurred in rural population due to indirect causes. On the other hand, the majority of deaths that happened in the urban areas were due to undetermined or unrelated causes of death. There was no difference was found in undetermined causes of death in both rural and urban population even though the number of deaths in both areas was the same. In summary, this result purported that direct causes play a crucial role in the overall population and indirect causes which highly affected this sample population is more likely to be preventable using different strategies.

A Further Possible Classification of the Data for the Meta-Analysis

Several studies and research on epilepsy-related deaths do not have common guidelines when it comes to distinguishing epilepsy-related deaths. There has been some research that categorizes several forms of death in different ways. For this study, we have distinguished epilepsy-related deaths into three categories. The first category is direct causes of death and these include status epilepticus and SUDEP. The second category is indirect causes of death and these include any damage or harm caused during a seizure. The third category is unrelated and or undetermined causes of death. An unrelated cause of death is when a person has other medical conditions along with epilepsy and the answer to the death cannot be defined which causes death. The final category of epilepsy-related deaths is undetermined causes of death and these are the ones when the cause of death cannot be figured out. Due to the lack of guidelines for distinguishing these deaths, it is quite easy to put different causes in the wrong ones. An example of that is how some studies on SUDEP have categorized SUDEP as an undetermined and or unrelated cause of death. Consequently, this happens because studies over the years have shown how researchers are still in the process of finding the root cause behind SUDEP. This study in particular has a holistic approach and looked into each cause of death in epilepsy mortality. The study evaluated if it is really possible to prevent these deaths and show that researchers or medical professionals could have a

Table 1: Pre Analysis Data.

Study	Total Deaths	SMR	Direct Deaths	Indirect Deaths	Unrelated Deaths	Area Type
Nicoletti et. al 2009	10	1.34	1	2	7	Rural
Banerjee et. al 2010	20	2.58	1	6	13	Urban
Mu et. al 2011	106	4.9	23	62	21	Rural
Ding et al. 2013	206	2.9	29	67	110	Rural
Ngugi et. al 2014	61	6.5	27	7	27	Rural
Granbichler et. al 2015	29	7.1	12	10	7	Urban
Keezer et. al 2016	189	4.28	44	6	139	Urban
Nicoletti et. al 2018	10	1	1	9	0	Urban

Table 2: Fixed and Random Effect of SMR on Epilepsy Related Deaths.

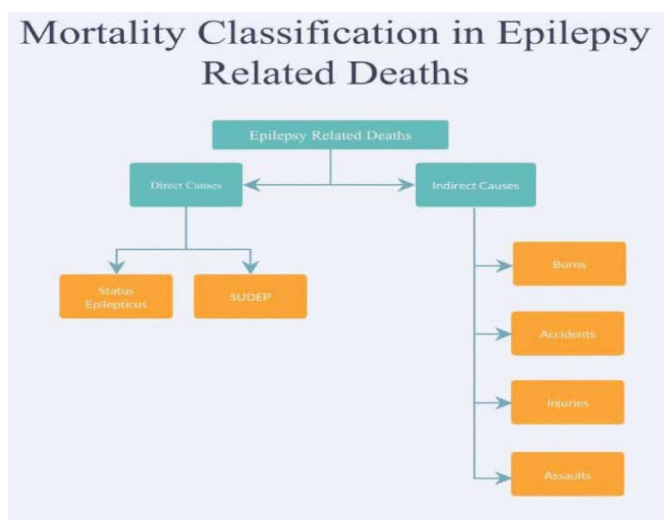|	Q	df	p
Omnibus test of Model Coefficients	8.278	1	0.004
Test of Residual Heterogeneity	1.647	7	0.977

Figure 2. Funnel Plot Correlation of the Standard Error and Observed Outcome.

Table 3: Wald Test Coefficients.

	Estimate	Standard Error	z	p	Lower Bound	Upper Bound
Intrcpt	1.658	0.576	2.877	0.004	0.528	2.787

general focus and touch on every bit for epilepsy deaths when diagnosing and providing information to PWE and careers.

Direct Causes

Direct causes of death in epilepsy are defined as deaths that occur due to the outcome of a seizure. There are only two conditions where the direct cause of death is possible and these include SUDEP, and status epilepticus. Almost all research on epilepsy looks into status epilepticus and SUDEP. The deaths due to direct causes are so far per research are not preventable because of its nature.

Sudden Unexpected Death in Epilepsy (SUDEP)

The term 'SUDEP' is defined as Sudden Unexpected Death in Epilepsy. This terminology was first discovered in 1997 in London. In the late '90s when this term was introduced, it was not that significant as much as it has been prioritized in the last recent years and still remains to be the most crucial topics in epilepsy-related deaths. SUDEP falls under direct causes of epilepsy. Furthermore, in the last few years, there has been a steep rise in death due to SUDEP and the cause behind it still remains unclear even till this day. Therefore, it is estimated that about half of epilepsy-related deaths are caused due to SUDEP. According to Edey, Moran and Nashef, recent studies on SUDEP has shown a 10-fold increase in mortality rates [23]. This rate is higher for women who are pregnant. In addition to that studies on SUDEP have shown significant relationships with other predicting factors. For instance, a research study on epilepsy mortality showed that 17% of deaths in that sample occurred due to SUDEP. The study demonstrated that adolescents are more at risk of mortality and there are multiple factors contributing to the cause [24]. The study quiet interestingly also reported the correlation of AEDs causing a higher risk of death. There are other studies that have shown that the risk of SUDEP varies based on the age group. In a pediatric study on SUDEP showed that children have a lower risk for SUDEP. However, mortality is significant among children because if SUDEP occurs in childhood then it is possible for children to go through the developmental delay [25]. A 9-year longitudinal study in a community setting in the UK reported that 93 cases in which 48 cases met the study criteria and deaths were preventable in this situation [26]. The major challenge in addressing SUDEP deaths is the aetiology and there has been research that has shown that the cause might be uncertain. This often leaves with confusion if SUDEP should fall under direct causes of death or undetermined

because it is a topic that is still being studied. Additionally, every researcher tries to approach the concern of SUDEP in a different way. For example, a study on SUDEP that had a genetic approach found that among 61 cases of SUDEP, 54 were definite SUDEP, 5 were probable SUDEP and 2 were definite SUDEP [27]. This study brought an interesting perspective to SUDEP classification because most studies just go by if the deaths were due to SUDEP rather than further classification. The study reported cardiac arithmetic and epilepsy genes causing SUDEP. Some studies have shown that the major causes behind SUDEP are indirect in nature and taking AEDs could lower the risk of SUDEP [28]. Literature and progress in SUDEP research have definitely shown that it is the current priority According to Thurman, Hesdorffer and French, a public health study on SUDEP reported that research has 'overemphasised' SUDEP in recent years. Most literature has cited that there is a major drawback when it comes to the awareness aspect of SUDEP. However, there have been some recent advances in the literature that there are biological markers that might cause SUDEP. Some of these potential factors include: breathing problems like apnea, heart rhythm, and other combined factors [29]. Thus, it is still debatable whether this is under one's control or not. Some of the etiological aspect or condition like heart problems could be easily mistaken and could be categorised as indirect causes of death. However, the key point that makes SUDEP as a direct cause is that these deaths are often unwitnessed and could occur during sleep or seizure during an activity. Thus, in certain way SUDEP is preventable by awareness and education to the general public, whereas for medical professionals and researchers it is significant for them to hold an approach that would help determine the cause behind SUDEP.

Status Epilepticus

The term 'status epilepticus' (SE) was introduced back in 1972. It is described as a serious medical emergency where a person gets subsequent seizures eventually leading to death. In other words, it is defined as "a condition when a person has continuous seizure lasting for more than 30 min, or two or more seizures without full recovery of consciousness between any of them" [30]. The seizures often happen one after the other without any proper baseline. It accounts for about 10% of the deaths among those with epilepsy. Besides contributing to death, it is also a leading cause of health care costs, morbidity, and mortality [31]. The condition is considered to be highly related to morbidity instead of mortality due to continuous seizures [30]. Studies have shown that prolonged SE could lead to permanent neurological damage. According to Sutter, Marsch, Fuhr and Ruegg, a study on 260 patients revealed that 38% of the deaths occurred due to SE. The study mentioned the relation of hypoxic encephalopathy and tumor puts one at a higher risk of SE [32]. In terms of demographics, some studies on SE have shown that children are more likely to be affected. According to Pujar, Neville, Scott and Chin, a population-based study with those with childhood convulsive status epilepticus showed the presence of pre-existing clinically significant impairments [33]. This study showed that children are more likely to die due to SE. There have been very old studies on SE, these studies in children had shown that mortality was among children was low and the leading cause was the etiology [34]. There were 7 deaths among 193 children. According to Meierkord et al., a mixed population study of 384 patients that included both adult and children showed that mortality in terms of brain damage was most common [35]. Majority of the deaths were common among females with cerebrovascular diseases. Another study on status epilepticus in France that comprised of 65 patients with status epilepticus showed that the incidence of SE was lower in children and the cause was dependent on etiology and age [36]. Overall, SE is considered as a direct cause of death to epilepsy even though the cause behind SE has indirect causes. The outcome from SE besides death could lead to permanent neurological damage or cardiac problems. Since it is more common among children, parents are responsible and should be aware of the risk factors. Hence, preventing death for a person having SE is about making people aware of all the potential risks. Prevention strategies could also be made by making sure people take AEDs regularly because significant research on SE management has found out that taking AEDs in a timely manner helps to prevent the risk of SE. Due to the severity of status epilepticus and lack of advanced research, it is something that

could not be controlled. However, one could minimize the risk of death by making people aware of it.

Indirect Causes

Indirect causes of epilepsy deaths mostly comprise of deaths that are accidental in nature like drowning, injuries, suicide and burns. In general, indirect causes of death could vary and do not have set terms. Studies on ERD focusing specifically on the indirect causes of epilepsy-related deaths could have an outcome of assaults to self-harm or there could be scenarios where two causes could go hand in hand. Besides the general population, maternity population was also affected due to indirect causes. According to Swiet, Williamson and Lewis, the maternal death rate was about .61/100000 people. Out of all the deaths, 6 were referred for neurological review and 1 did not follow doctors' advice provided to them about managing their epilepsy. These causes are sometimes based on culture and other factors as well. Furthermore, most studies that focus on comorbidities report that the cause of death is beyond SUDEP, status epilepticus and other popular terms for ERD. This could be inferred from a study done on excess mortality based on comorbidities and major determinants. The total number of deaths occurred in this study was 266 out of which 6.8% (18 deaths) were direct causes of death,17.7% (39 deaths) died from heart diseases and 71.8% died from cerebrovascular diseases [37]. The study concluded that comorbidities and underlying conditions were major determinants of death. Some studies have also mentioned comorbidities cause's premature deaths in PWE. According to Kaiboriboon, Schiltz, Bakaki, Lhatoo and Koroukia, a study comparing premature mortality in low and high-income areas among adults with epilepsy studied mortality and cause of death in 12630 deceased subjects [38]. The cohort analysis of the study showed a mortality rate of 18.6/1000 persons and SMR of 1.8. Additionally, there were about 10% of the deaths that happened due to direct causes of ERD and conditions such as cardiovascular diseases, cancer and accidental injuries were common causes in the cohort. Thus, comorbidities play a role in premature death in ERD.

Accidents

The term accident is defined as an eventful event that could have been prevented. People with epilepsy are more prone to accidents due to the nature of the disease because the majority of the time the person would be unconsciously doing something. An example of an accident is a person riding public transportation like the train and when their stop comes they take the wrong step and fall on tracks. Research on accidents and epilepsy mortality has shown association as well. There have been a few studies that confirm all accidents are caused due to psychiatric comorbidities. Furthermore, the deaths caused due to accidents could be reduced by public health awareness, and a holistic treatment approach when diagnosing epilepsy. Another example of death could be a person getting out of a moving car during their seizure in a traffic signal and another car might cause an accident. This is similar to the example above where the PWE could inform the person closest that they will be having a seizure and need help. Something that makes these deaths in this population tricky to prevent is the nature of accidents itself. Moreover, it could get very challenging for a driver to slow down their speed or pull over a car all of a sudden. Deaths under this kind of indirect cause are tough to prevent. However, the only effective way to prevent these deaths requires the PWE to make the person closest to them aware that they are about to get a seizure and will be needing help to make sure they are safe until they gain consciousness.

Drowning

The World Health Organisation defines drowning as "the process of experiencing respiratory impairment from submersion/immersion in liquid" [39]. It is known to be one of the most common indirect causes of death and is known to affect all major age groups. According to Byard, the risk of drowning is 15-19 times higher in people with epilepsy which examined the issue by studying dead bodies recovered from the water [40]. Another study on drowning with people with epilepsy has found that these deaths could actually be prevented in advance if people with epilepsy and careers

are informed in advanced [41]. In this study, Bell and colleagues studied 51 cohorts of people with epilepsy who died of drowning. The outcomes of the study found a high SMR of 18.7 and out of the 88 deaths 4.70 were expected. As drowning is known to affect people of all ages, it is known to be a fatal risk factor in those with children. For example, a cross-sectional study of 0-14 years of age found out that 16 out of 19 deaths were due to drowning during a seizure. The median age for the study was 8years and hence known to affect children because of their pre-existing medical condition of epilepsy. Some studies have shown that drowning usually happens in low-income areas and prevalently due to natural geographical causes like rain and floods. For example, a study in rural Bangladesh examined accidental deaths in PWE. In this study, there were 12 deaths due to accidents out of which only 10 were due to drowning. This study explained the key importance of taking safety precautions that should be taken during floods in order to prevent these deaths among PWE.

Injuries

The WHO defines injuries as harm or damage due to collisions, drowning, poisoning, falls or burns and violence [42]. People with epilepsy who die due to injuries are often categorised as an indirect cause of death. They are mostly known to occur in rural and other low-income areas. According to Boschine et al., a study on the role of seizures in brain injury in sub-Saharan Africa found that adults with epilepsy were more likely to die due to a brain injury. The study described the findings through descriptive analysis and suggested that more information should be provided in overall brain injury for those with epilepsy [43]. Some studies highlight that burns injuries are preventable in high-income countries [44]. A research study on mortality risk factors and causes in epilepsy deaths had found that burn injuries are the third-largest cause behind epilepsy-related deaths. In their 30 year follow up study, a cohort of 164 patients with epilepsy had about 41 people dying due to burns. These burns mainly occurred during cooking as a result of direct flame. Another study on epilepsy aetiology studied treatment outcome and management of burns on PWE. This cross-sectional study included 41 participants from October 2011 to April 2012 where 19.5% of deaths occurred due to burns. These injuries due to burning occurred due to kitchen flames as well. These studies have concluded that burn injuries could be preventable by monitoring the patient.

While there are high-income countries where studies have found that accidental deaths due to injuries are high as well. According to Mateen Shinohara, Alan, Black and Streatfield, a population-based study in Matlab in Bangladesh found that accidental deaths are higher in high-income countries when data on accidental injuries were compared between people with and without epilepsy from 2005 to 2008 [45]. Significant studies have also shown that injuries could be higher for those who might have a certain type of seizure. According to Pooya, Nikseresht, Yaghoubi and Nei, a study on physical injuries with PWE looked into the risk factors of injuries [46]. The study comprised of people who were 18 years and older with active epilepsy for about a year. The findings of the study mentioned that 8.7% were severe injuries, 44.3% were minor injuries. The studies concluded that all of the injuries were significantly related to general tonic-clonic seizures. Other studies have shown how gender and certain age group are affected by it. For example, a study on burn injury focusing in developing countries found that out of 39 deaths of PWE, 26 were female and the average age was 36 years [47]. Briefly, burns as a risk factor might be preventable in some instances and in some instances, it would be different. Certainly, there have been studies that show the risk of death is low among PWE. According to Chang, a study looked into the trends in deaths due to injury in the US which showed that the risk of fatal injury among PWE decreased from 1981-2010 and the comparison between the general population and PWE confirmed that PWE had a lower risk of dying from injury [48]. There have been studies that have shown that epilepsy deaths are preventable easily in children by monitoring whereas in an adult population it might be something different.

Self-Harm

Self-harm as a risk factor of epilepsy-related deaths mainly arises due to the preexisting comorbidities of epilepsy. Hence, deaths due to comorbidities

are more likely to cause premature deaths in PWE. Some injuries are known to contribute in the form of injuries. For example, when a person unconsciously bites their tongue during a seizure is both an injury and self-harm and deaths due to tongue biting could be difficult to prevent due to the seizure safety. Another form of self-harm commonly found in ERD is a drug overdose. According to Meyer, Voysey, Holmes, Casey and Hawton, a self-harm study data from 1994-2008 included 132 PWE and 9778 people without epilepsy [49]. The rate of self-harm in the study was about 2.04 and more likely to happen due to antiepileptic drug overdose. The interesting factor in this study was that the overall method of self-harm in both the population was the same in both groups. Certain studies on self-harm with ERD have highlighted how it affects the overall cost of treatment. For instance, a 10-year longitudinal study in Australia in children who died of assault or self-harm revealed that 71.8% of children in urban areas had died compared to 27.5% of people in rural areas [50]. About 26.6% of deaths out of the overall population in the hospital occurred in those with epilepsy. Findings of the study also revealed that the gross amount of money that went into hospital treatment £13.6 million for AED or poisoning among ERD. Significantly, the study findings revealed that the majority of the patients deceased were 11-16 years of age. Thus, it could be challenging to prevent deaths due to self-harm because of its association with psychiatric comorbidity.

Assaults

An assault in a person with epilepsy is defined as unwanted physical harm usually when a person is having a seizure. Deaths due to assaults have a small number in mortality. Most of these deaths usually happen in both low and high-income areas. These deaths are known to happen in the workplace which also includes harassment. Women are more likely to be affected by these than men. A 10-year longitudinal study done on women examined sexual assault over the period of time. The findings of the study showed that the SMR for these deaths was about 2.9. The authors of the study confirmed that assaults within those with epilepsy contribute to a smaller number of deaths compared to other chronic illness [51]. Deaths due to assaults are fairly new in epilepsy mortality and it definitely needs more attention because there is a possibility to prevent them.

Suicide

Suicide in those with epilepsy is defined as a condition when someone attempts to harm themselves and eventually kill themselves. According to the CDC, it is defined as an act of injuring oneself with intent to kill themselves [52]. Suicide falls under indirect causes of death. It is considered as one of the most common factors of death in PWE. Suicide is known to happen in both low and high-income areas. In order to understand the significance, there have been studies that compare the suicide rate in those with epilepsy and the general population. The U.S national study on suicide had subjects from 17 states where the average suicide rate was 16.89/ 100,000. The suicide risk was also 22% higher than the regular population [53]. However, data from this literature reveal that the rate is pretty low compared to the other causes of death with those who have epilepsy. Several studies on epilepsy and suicide also claim that the rates of suicide are underestimated. Based on the basic understanding of suicide it is something that is preventable. Significantly, a study was done on the older age population (40 to 49 year old) reported that the deaths occurred due to poisoning [53]. The literature on suicide has confirmed that there is a strong relation to mental health issues with suicide. According to Gail and Sander, suicides in epilepsy are initiated by psychiatric conditions. One of the most challenging issues in suicide is predicting whether the person is suicidal and future studies need to address this through assessment [54]. The causes of suicide in people with epilepsy are potentially related to medications. For example, a community-based study on suicide and anti-epileptic drugs showed that there is a high correlation between AEDs and suicidal ideation [55]. The findings of the study revealed a very high SMR of 5.1 and that AEDs should be carefully prescribed [55]. On the contrary, there have been studies that hold that there is no relation between AEDs and suicide. According to Hesdorffer, Ishihara and Webb, a population-based study that had 14059 patients with epilepsy and 56184 patients without epilepsy showed no relation of AEDs and suicide

attempts [56]. This study demonstrated the 5 fold increase in the risk of suicide and how aetiology still remains an unknown mechanism. Some literatures on suicide and epilepsy have shown that most of these deaths occur due to the side effects of medication leading to other mental health condition. Hence, communicating the risks of suicide during the treatment could be beneficial to the patients, and their family.

In summary, the indirect causes of death include drowning, suicide, assault, self-harm, and accidents. From the studies above, it could be inferred that deaths due to indirect causes of death are actually preventable and this would take awareness, safety precautions and having an eye out for potential accidents on PWE. Medical professionals play a huge role in this as they would be the first one to provide knowledge and information on how a person might be at a high risk of potential deaths and hence prevent these deaths by talking to people.

Overall SMR rate for the indirect cause was significantly higher in rural areas. People in urban areas should be informed more about epilepsy-related deaths because most deaths in this population are direct causes were carers or PWE look forward to being more informed about mortality risk factors. Additionally, strict measures should be taken to safeguard PWE from being assaulted or being harmed because most studies that have happened in rural areas due to cooking flames could potentially be prevented under supervision looking at the age group of people who are usually affected are children and young adults. Medical professionals should also think about the comorbidity factors when prescribing medications since most of them have side effects that could lead to accident or harm and think about pregnant mothers with their newborns.

Conclusion and Evaluation

The findings of this study showed a positive influence of SMR and direct causes are the leading reason behind epilepsy-related deaths (ERD) in the overall population. More than the prevalence of epilepsy, it has been very shocking to see how the death rates have spiked and recognise if these deaths are actually preventable or not in addition to making sure to define all the possible causes of death in epilepsy. From this study, it could be inferred that the majority of the deaths in epilepsy are preventable based on the scenario. This is partly because indirect deaths were relatively higher in both rural and urban areas and these are usually preventable. The study also laid out a complete breakdown of different forms of death in epilepsy mortality which is very often misunderstood due to lack of proper criteria to classify them. According to Devinsky, Singh and Friedman (2018), the major issue that research in epilepsy mortality faces worldwide is the fact of how inaccurate data is recorded for mortality in ERD in any given country. This shows that the procedure lacks to effectively studying epilepsy risk factors for death. In brief, the different causes of death in epilepsy that were discussed previously include direct, indirect, undetermined and unrelated causes. The direct causes of epilepsy are defined as deaths that are a consequence of a seizure. These causes include SUDEP, and status epilepticus. On the other hand, indirect causes of death are the ones where people get harmed as a consequence of a seizure, and the harm could be in the form of burns, injury, and assault etc. The other category is undetermined causes and these are deaths that could not be defined research still needs to address these challenges. The final category is the unrelated causes, where the cause of death is completely irrelevant to epilepsy. The SMR rate did not differ much in terms of both urban and rural areas. The indirect causes of death in rural areas were higher, whereas direct causes showed a significant factor to contribute to the overall death rate. The unrelated and undetermined causes of death were almost the same in both populations. This further explained that studies on mortality should be focusing on having a general approach rather than being particular and overemphasising on SUDEP in particular. This would help to come up with different strategies to prevent these deaths as well. Furthermore, this would prevent carers or PWE to not say that they were not aware of the potential death risks. Since the number of deaths in other causes besides the direct causes were relatively higher, it could be inferred that these deaths are preventable by

education, raising awareness, and safeguarding PWE. On the other side, the direct causes of epilepsy-related deaths are the major contributing risk factor for death in urban areas. In order for deaths to be preventable in terms of geographic and demographic location, efforts should be made to have equal access to treatment rather than having disparities due to income and population. This study has demonstrated that there is a need for evaluating the risk factors when diagnosing someone with epilepsy. It could be an extra step, in addition to the diagnosing process, and would look much like an assessment for mortality risk factors. This assessment would help figure out the kind of death a person might potentially fall under will help clinicians and professionals to come up with an assessment of preventive interventions. This step would look into evaluating the risk factors for death and would look more into co-morbidities, medication, and other conditions the person might be having. During this study, it was found that most research focused on how these direct causes are not well explained by medical professionals to PWE and carers. During the screening process for this study, it was found that most studies looked at the adult population rather than the pediatric. Some studies also showed that deaths in the older age group for PWE was significantly larger, due to poisoning and therefore this also has a chance to be prevented. Most of the studies used in the meta-analysis for this study looked into all age groups of people and during the screening process of selecting articles, it was found that there were not enough studies in the older age group for PWE, which could be another area of interest for a future research topic. Due to the study criteria, there were only 8 studies that met the requirement. This explained that there were very few studies that focused on SMR and most studies that were excluded from this study focused on the same country. This means that future studies should look into other countries. In addition to that studies examined the unrelated and undetermined causes of death in this population because this somewhat overlaps with SUDEP. Thus, some studies also failed to compare different causes of mortality in different age groups. The majority of studies that were excluded approached mortality specifically by looking into SUDEP, rather than focusing on death as a whole. Potential mortality-related studies on this topic should cover the premature mortality aspect of death because it is much different from this topic. One of the major drawbacks of this study was that despite classifying the various causes of death, the analysis does not include an in-depth detail on the form of deaths. Another drawback of the study was that the data did not have details on gender. This would be a potential area for research to learn the various risk factors and whether they vary in terms of gender. While diagnosing epilepsy could be a long time-consuming process, people often do not realise how one falls into a greater risk of death due to the other factors from having epilepsy. It is also one of those diseases that take a long time because it gets misdiagnosed majority of the times. It would be ideal to implement something within the treatment to make sure that the risk factors do not get undiagnosed. Interestingly, people who are newly diagnosed and whose epilepsy is controlled are less likely to be prone to death (National Institute of Health, 2019). Current challenges in epilepsy-related deaths are to figure out what potential risks would be applicable to a person because most people are made aware of SUDEP, but they might not be aware of other kinds of deaths that a person might potentially be at risk. It would be very interesting to learn how the focus of epilepsy mortality would change and lead to a direction in the next few years. Over the years there has been a lot of improvement when it comes to preventing epilepsy-related deaths. Most literature has suggested an urgency to make it a priority for medical professionals to communicate the significance of informing families and carers of potential death risks for those with epilepsy. Most importantly a significant gap in this is that not all the potential causes of epilepsy-related deaths are disclosed to the family or carers. Instead, these professionals tend to touch on little bits and pieces like status epilepticus or SUDEP. Furthermore, it would be beneficial if these professionals addressed this issue as a whole. Medical practitioners should inform PWE and carers about every possible risk factors for epilepsy mortality, whereas researchers in this area should have an analytical approach when classifying the different forms of deaths in epilepsy. Furthermore, figuring out the root causes behind epilepsy will also help medical professionals to design an effective treatment option for the diagnosis. The statistics used here showed that there is a need for consistent data collection and comparison studies in this particular research topic that would help to address this issue. This study found that deaths in most cases are preventable but it needs effort in terms of awareness for the public, and an extra step during the diagnosis stage for assessing any death risk a person might have, based on their seizure and other co-morbidities. Overall, this study comes up with a clear understanding of different causes of death and realistically asserts these deaths could be prevented or not.

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