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Degree project
Title: Detection of poststroke epilepsy and accompanying anti-seizure treatment using Swedish national registers – a validation study

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Degree project: 30 credits
Program: Program in Medicine
Year: 2021
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Abstract

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Key words: Poststroke epilepsy, validation of registers, anti-seizure medication

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Introduction

Stroke is the most common cause of epilepsy, causing an estimated 14-21% of all epilepsy cases. Unfortunately, there is limited knowledge regarding the optimal treatment for post-stroke epilepsy (PSE) and there has been done few studies on PSE because of the difficulty in following elderly patients with multimorbidity over time; epileptic treatments can continue for years and many studies on the field has only evaluated 12 months. Swedish National Patient Register (NPR) can give unique possibilities in following large patient cohorts over a long term, but to know whether certain conclusions from register studies are accurate, it is important to validate the registers.

Aim

The goal of this study was to evaluate the accuracy of register-based criteria associated with post-stroke epilepsy in the Swedish NPR.

Methods

This was a retrospective validation study with a total study population of 177 deceased individuals who have been identified by The Swedish National Board of Health and Welfare that fulfiled register-based criteria of PSE. Medical records from these patients were examined thoroughly to see if stroke and subsequent epilepsy could be confirmed, and the collected data were filled into protocols. The data were analysed and positive predictive value

(PPV) was used as a method to validate the outcome, calculated as a ratio between the number of patients who had likely or definite epilepsy after stroke to the total number of patients.

Results

From the 177 patients who were identified, a total of 133 (PPV: 75%, 95%CI 0.69-0.82) had epileptic seizures after stroke. 105 out of 133 epileptic patients were prescribed anti-seizure medication (ASM).

Conclusions/implications

The results of the study are informative for future register-based studies on PSE. Compared to another recent study validating epilepsy codes in several countries, this result can be seen as high: in our study, at least 75% of the identified patients actually had PSE. Considering the risk of misdiagnosis in epilepsy, register studies will always identify some patients who do not meet the diagnostic criteria for PSE.

The accuracy of the register codes may be further increased by requiring that the patients had received an anti-seizure medication, or to only identify patients diagnosed with epileptic seizures; our study also included unspecified seizures which identified some patients who had experienced seizures unrelated to epilepsy.

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List of abbreviations

PSE - Post-stroke epilepsy
ASS - Acute symptomatic seizure
ILAE - The International League against Epilepsy
ASM - Anti-seizure medication
NPR - National patient register
IPR - Inpatient register
EEG - Electroencephalogram
cEEG - Continuous electroencephalogram

1 Introduction

Definitions and prevalence

Epilepsy is one of the most common brain conditions, affecting more than 70 million people worldwide and an estimated 1-3 % of the population. It is defined as a chronic central nervous system disease characterized by spontaneous recurrence of unprovoked seizures caused by abnormal brain activity [1]. Common clinical manifestations of seizures are sensory phenomena, recurrent muscle twitching or behavioural arrest, with or without loss of consciousness [2,3].

The International League against Epilepsy (ILAE) defined epilepsy in 2005 as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure” [4].

Whereas all people who have epilepsy experience seizures, not all with seizures have epilepsy. Provoked seizures may occur after an acute insult (for example, stroke or hypoglycemia) and are acute manifestations of the event. These seizures may not recur once the acute phase is over. On the other hand, an unprovoked seizure is a seizure that occurs in the absence of any obvious instigating factors, or occurring more than 7 days after an ischaemic and/or haemorrhagic stroke. Post-stroke seizures have been classified as occurring either immediately before, after (within 24 hours), or of early or late onset. Early-onset seizures, also known as acute symptomatic seizures, are considered to be provoked when they occur within one week after the event [5, 6].

The incidence of epilepsy has a bimodal distribution, with the highest risk in infants less than one year and older adults above 50 years of age. In older adults, the incidence increases with age and the highest incidence is found in those above the age of 70, which reflects the higher stroke frequency [7]. The overall most common identifiable cause of epilepsy and seizures in older adults is stroke and causes an estimated 14-21% of new epilepsy cases [8]. In the

elderly population over 60, stroke is estimated to account for 30-50% of newly diagnosed cases of epilepsy [9]. The prevalence of post-stroke epilepsy (PSE) in adults after stroke has been shown to be around 2-4% [10].

ILAE published a revised classification of seizure types in 2017, dividing seizure types into three different categories: Focal onset (previously called partial), generalized onset and unknown onset. Focal seizures are limited to one cerebral hemisphere and appear to arise in a localised area of the brain and the symptoms will depend on which part of the brain is affected. Generalized seizures begin in both hemispheres in bilateral neural networks. A seizure can also begin focally and then later spread across the whole brain, resulting in a generalized seizure. When the beginning of a seizure is not known, it is classified as an unknown onset seizure [11].

In the past, the most commonly used definition of epilepsy was two or more unprovoked seizures occurring greater than 24 hours apart. In 2014, however, ILAE presented a practical definition of epilepsy in circumstances where the criteria for two unprovoked seizures were not met [12]. The new definition of epilepsy is an individual meeting any of the following conditions: 1. At least two unprovoked (or reflex) seizures occurring >24 h apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome.

This change has to a certain degree blurred the meaning of epilepsy and seizures in conditions where the probability of subsequent seizures is unclear [13]. Regarding seizures after stroke, data have shown a high recurrence risk (50-90%) [7, 14-17] but this risk rate has not been consistently found in all studies. However, ILAE argues that the recurrence rate of a single unprovoked seizure for patients after a brain insult may be comparable to the risk after two unprovoked seizures and therefore fulfils the epilepsy diagnosis criteria.
Berges et al. [16] retrospectively analysed data from 3205 patients admitted for a first-ever stroke between 1984 and 1994. From this pool, they found 159 patients, 4.96%, who had experienced seizures and from these 50.3% had at least one seizure relapse. Sung et al. [17]

found a recurrence risk of 90% for late-onset seizures (>2 weeks after stroke) but only 35% for early-onset seizures (≤2 weeks).

The difference between unprovoked and acute symptomatic seizures

Acute symptomatic seizures (ASS) are defined as seizures occurring during a systemic insult or in close proximity to a central nervous system insult and are considered situational. These insults may be infectious, metabolic, toxic, or inflammatory in origin. It is important to make a distinction between ASS and epilepsy since it underscores different pathophysiological causes, as well as prognosis and treatment. The most frequent causes of ASS are intracerebral infections, cerebrovascular diseases, head injuries, and toxins: especially alcohol. A seizure occurring in near time to an acute insult should be classified as an acute symptomatic seizure - even if the individual has epilepsy - because the cause of the seizure is more likely due to the insult [18].

The Commision on Epidemiology and Prognosis decided to keep the term "acute symptomatic seizure" as different from an unprovoked seizure. Beghi et al. published a guideline in 2010 in order to help epidemiological studies determine the circumstances when a seizure should be classified as acute symptomatic [19]. They identified several ways in how acute symptomatic seizures differ from epilepsy. First of all, these seizures do not have a predisposition to recur unless the underlying acute cause recurs. Secondly, there is a clearly identifiable cause of these seizures. The temporal sequence makes causality likely for ASS when they occur in near time with conditions such as a stroke or head injury.

After the patient has experienced an ASS, temporary use of anti-epileptic medications (ASMs) may help suppress seizures while the underlying etiology is still present [18]. Prophylactic ASMs reduce the risk of acute symptomatic seizures within the first week after head trauma, but there is little evidence that this changes the risk of epilepsy. Factors that influence if treatment should be given are recurrent seizures, fragile clinical condition and blood located close to the cortex. Because ASMs have not been proven to reduce the risk of developing epilepsy and also carry the risk of potential side effects, ASM treatment for acute symptomatic seizures is in most cases short. The praxis of how long to treat patients with

ASS with ASMs varies and should be individualised for every patient depending on the underlying disease, clinical situation, severity of the seizures, as well as the risk of further seizures [19].

Predictors for post stroke epilepsy

In adults, factors that increase the risk of PSE include stroke severity, the volume of infarcts (the larger the stroke, the higher probability of PSE), location of infarcts (cortical engagement has a higher risk of PSE), and stroke subtype [20-22]. In a study by Misirli et al., cortical involvement was found to be the most important risk factor for the development of seizures with an odds ratio of 4.25 [23]. In adults, Jungehulsing et al. found that stroke severity and hypertension were significant predictors for PSE, but found no relation between some metabolic factors and the development of seizures [24]. In contrast, Devuyst et al. found that an elevated level of cholesterol may have a protective role in seizures [25].

Most studies show a twofold risk of epilepsy after a brain haemorrhage compared to a brain infarction, which agree with the results from a meta analysis where the odds ratio for epilepsy after brain haemorrhage was 2.41 [26].

The SeLECT score

The SeLECT score is a validated prognostic instrument for late seizures after stroke [27]. It generates an individualised estimate for the risk of late seizures (>7 days after ischemic stroke) within the first years after the event. The model incorporates 5 different risk factors for PSE: cortical involvement, severity of stroke, early seizures, large-artery atherosclerosis, and the territory of middle cerebral artery involvement. Severity of stroke is defined by the NIHSS-score at admission, and it makes an estimate based on the intervals <3 points, 4-10 or >11 points.

Pathogenesis of seizures after stroke

Seizures after stroke vary in pathogenesis depending on the onset. In early-onset seizures, an accelerated release of excitatory neurotransmitters and local metabolic derangement lead to

electrophysiological instability and neurotransmitter imbalance. Electrophysiological instability may also result from acute hemodynamic changes that disrupt the increase in intracellular calcium and sodium [28].
After the stroke, there is a set of acute hemodynamic changes that disrupt the local area - reducing neuronal stability and causing abundant discharges. Ischemia has been shown to increase local intracellular sodium and subsequently lower the threshold for cell depolarisation by causing a sodium pump failure. When the accumulation of sodium inside the cell reaches a certain point, calcium channels will be activated leading to a sudden influx of calcium with a resultant seizure [29].

PSE can result from a combination of factors including genetics, inflammation, glial proliferation, metabolic disturbance, and neural network reconstitution. The neural network consists of nerve fibers, synapses and neural circuits, and PSE reflects a structural change in neuronal networks developed after the cerebrovascular injury. Seizures after cerebral haemorrhages are hypothesised to be because of haemosiderin deposits that cause an increased neuronal excitability, or because of gliotic scarring [29]. Glial proliferation and activation occurring after a stroke could also play a role in epileptogenesis. Activation and proliferation of astrocytes in the cortex likely leads to dysfunctioning of the ion channels, resulting in cell depolarisation, increased glutamate and lowered GABA - all of which promote PSE seizures [28].

Diagnosis of possible seizures in stroke patients

When the patient has experienced a possible seizure, the clinician's first diagnostic step is to determine if the event is caused by epilepsy or one of the myriad of possible differential diagnoses. The elderly population is at risk of several conditions that can mimic seizures. Differential diagnoses include syncope, psychological disorders, parasomnia, movement disorders, and more.
Misdiagnosis rates in epilepsy are high; of patients who were diagnosed with refractory epilepsy whose diagnosis was reviewed at an epilepsy center, 20-30% were found to be misdiagnosed [30].

The diagnosis of PSE depends on the onset of the seizure, as described above. If the first seizure occurred within a week after the event, it is considered to be ASS and therefore not indicative of PSE. On the other hand, a seizure occurring more than one week after a stroke is considered unprovoked. This infers a >60% risk of further seizures and therefore fulfils the diagnostic criteria for epilepsy according to the latest definition recommended by the ILAE [12].

The distinction between early and late seizures is not always straightforward. The cerebrovascular situation may have been unstable, and it can be difficult to determine if the stroke has worsened at a later stage than at the initial onset or if there is another provoking factor. Also, the exact time of stroke may be unknown. It is therefore important to be certain that the seizure is unprovoked before giving the epilepsy diagnosis. If there is uncertainty about the seizure, it may be better not to diagnose PSE but rather have a watchful waiting approach since there is no clear evidence of a >60% seizure recurrence risk [28]. A detailed history is essential in establishing the underlying cause: important clinical features to take into consideration when meeting the patient include event description, associated neurological features, speed of onset of prodromal symptoms as well as a careful examination. However, sometimes clinical information and patient history is not always enough to lead to a clear diagnosis; in such cases, electrocardiography and a 24-hour video electroencephalogram (EEG) can help. A normal EEG recording cannot rule out epileptic seizures because some types of seizures, such as frontal lobe epileptic seizures, may show negative findings. Video recording EEG and electrocardiography as a combination is thought of as the "gold standard" for differential diagnosis [31].

In the early phase following stroke, EEG is an important diagnostic tool to detect electrographic seizures. Continuous EEG monitoring (cEEG) can be used to detect seizures in critically ill patients who only show subtle clinical findings, such as mild facial twitching or focal sensation changes. cEEG should be initiated hastily when non-convulsive seizures are suspected [32]. When cEEG was performed in patients with acute brain injury, 92% of seizures had no clinical manifestation, and 9% of patients with acute ischemic injury experienced non-convulsive seizures [33].

Consideration of Treatment and prognosis

Treatment for PSE is generally symptomatic. There is a lack of studies that prove that prophylaxis will prevent seizures. Most studies have assessed the role of ASMs in patients with epilepsy of various etiologies, but there is very limited data that have specifically evaluated ASMs role in PSE. There is no consensus on the ASM choice for PSE, and the decision should be tailored to each patient based on individual factors such as age, comorbidities and side-effect profile. PSE typically occurs in the elderly population. It is general practice that when a patient presents with a second recurrent seizure, ASM should be initiated [28].

A recent study in PSE patients found that 27.1% of patients who received ASM treatment after the first epileptic attack developed seizures 1 year after, whereas 53.8% of patients without ASM treatment did at the same time [34]. The authors concluded that ASMs should be recommended for PSE patients. Both classic (valproate, phenytoin, carbamazepin, and phenobarbital, etc) and new ASMs (lamotrigine, oxcarbazepine, topiramate, levetiracetam, etc) are used [35]. ASMs exert their antiepileptic effect through regulation of neurotransmitter imbalance, as well as sodium and calcium channel retardation [35].

A multi-center questionnaire survey on the treatment of PSE in Japan found that Carbamazepine was the most commonly used ASM in the country, followed by valproate and levetiracetam [36]. Malerba et al. evaluated the prescription pattern of ASMs in Italy for refractory epilepsy and found that Levetiracetam (35%), Carbamazepine (34%) and Lamotrigine (30%) were the most commonly prescribed ASMs in adults [37].

A randomized, non-controlled study by Gilard et al. compared the efficacy and side effects of Carbamazepine and Lamotrigine for PSE by measuring seizure freedoms over a 12-month span, and found the latter medication to be more efficacious and the patients treated with it reported fewer side effects [38]. Another similar study by Consoli et al. instead compared Carbamazepine and Levetiracetam [39]. A meta-analysis of these trials showed no difference in efficacy between Levetiracetam and Lamotrigine regarding seizure freedom, but found a greater rate of adverse effects occurring with Levetiracetam [40].

In terms of prognosis, PSE is often described as a form of epilepsy that is easy to manage, and monotherapy is in most cases sufficient to control seizures [41]. Stephen et al. followed the treatment response for PSE patients for 2 years and found that the majority of the patients required only one ASM and at the end of the second year, up to 67% of the patients were seizure-free [42].

Adverse effects of ASMs

When selecting an appropriate ASM for older adults, taking efficacy into consideration is not the only factor. The decision to choose the most suitable drug has to be individualized according to the patient's sex, comorbidities, age and other medications that have a potential for interaction. Generally, patients with PSE carry risk factors for cardiovascular disease, take other drugs (such as statins, anticoagulants), are likely to be >65 years of age and have remaining neurological deficits after the stroke incident [28]. The ideal ASM should therefore have as low a detrimental effect on vascular disease as possible, e.g. no effect on surrogate markers that are associated with increased risk for cardiovascular accidents. In addition, it should be well-tolerated, safely administrable for patients with hepatic or renal failure, and have no relevant drug interactions.

Enzyme-inducing ASMs such as carbamazepine, phenytoin, primidone, phenobarbital have been shown to increase biochemical markers of vascular disease, such as total cholesterol, c-reactive protein, homocysteine, lipoprotein. Also, they can increase the hepatic metabolism and thus decrease serum concentrations of other co-medications - some that are used in post-stroke patients (e.g. warfarin) [28]. ASMs that are not metabolised by the liver, such as levetiracetam, are more appropriate in patients with hepatic disease, whereas with patients suffering from renal failure; Carbamazepine and valproic acid are preferred [43].

Psychiatric adverse effects can be especially relevant in those with a history of psychiatric conditions. In the wake of a stroke, depression is also common. Both Levetiracetam (22%) and Zonisamide (10%) have a notable risk to induce behavioural adverse effects [44]. Especially Levetiracetam has been found to have a detrimental effect on behaviour, making

this ASM less appropriate in patients with psychiatric comorbidity or suffering from post-stroke depression.

Cognitive decline generally increases with age, and is more common in older adults. Negative impacts on cognition have been noticed, especially with older ASMs that were developed before 1990: such as Carbamazepine, Phenobarbital, Valproate and Phenytoin. The most prominent negative impact was seen with Phenobarbital. Most “newer” ASMs such as Lamotrigine, Levetiracetam and Gabapentin have been found to have less adverse cognitive effects than Carbamazepine [45, 46].
With chronic use, several ASMs have the side effect of osteoporosis. Enzyme-inducing ASMs as well as Valproate may increase the risk for fractures. Enzyme induction can result in an accelerated metabolism of vitamin D and increased bone turnover [43]. For Valproate, its bone-depleting ability comes from interference with osteoblast function [47]. General recommendations are to encourage regular exercise habits as well as to supplement diets with vitamin D and calcium. It is especially important to be cautious when prescribing the mentioned ASMs for older women who have risk factors or a history of osteoporosis.

In 2008, the FDA issued a requirement for all ASMs to carry a label warning of increased suicidality. This decision was based on a meta analysis the FDA did in 2008, analyzing results from nearly 200 randomized clinical trials done before 2008 that assessed the efficacy of many drugs including 11 ASMs compared to placebo. The ASMs analysed in the study include Lamotrigine, Levetiracetam, Gabapentin, Carbamazepine, Valproate and more. The analysis concluded that compared to placebo, ASMs increased the suicidality risk nearly twofold among patients treated for epilepsy, psychiatric disease and other diseases. And for patients treated for epilepsy, the suicidality rate was 3,4 of 1000 with ASMs compared to 1 of 1000 with placebo [48].
Almost all ASMs approved even after 2008 are mandated by the FDA to carry this label. FDA’s meta-analysis has been criticised for being subjected to methodological limitations, such as grouping all ASMs together despite having varied risks, where 7 out of 11 ASMs had statistically nonsignificant increases and 2 showed a decrease. A new meta-analysis carried out in 2021 by Klein et al. showed that for 5 new ASMs approved since 2008, no significant evidence was found for increased suicidality when treated for epilepsy [49].

Individuals suffering from epilepsy have increased suicidality and depression in comparison to the general population, especially in those individuals with uncontrolled seizures. In a case-control study by Christensen et al., it found a more than threefold higher risk of suicide for individuals with an epilepsy diagnosis [50].

The importance of validating registers

The literature regarding post-stroke epilepsy is surprisingly scarce, mainly because of the difficulty there has been in following elderly multimorbid patients over time. Real world data provide an alternative. By using information from health and prescription registers, research groups have been able to follow given antiepileptic treatment and how it affects the outcome of the patient's epilepsy. However, register-based studies have caveats. Compliance with dispensed drugs and accuracy of diagnostic codes are some possible limitations.
If the investigated variables have high validity, then the same method can also be used to identify a large cohort of patients for future studies that could be of importance for epidemiological knowledge and the optimization of anti-seizure treatment.

Swedish register used in the study

The National Patient Register (NPR) contains data from all the visits made in both in- and outpatient specialist health care. In Sweden, healthcare is accessible to all inhabitants. Reporting to the national health registers, which are managed by the Swedish National Board of Health and Welfare, is mandatory and the register has a nearly complete coverage of the population. NPR includes all inpatient care in Sweden as well as outpatient doctor visits from public and private caregivers. For each health care visit, the register uses one main diagnosis and up to 21 secondary diagnoses determined by the patient-responsible physician using the Swedish International Statistical Classification of Diseases and Related Health Problems 10th edition (ICD-10) coding.

History and coverage of the NPR

The NPR was established in 1964, but it took until 1987 until it had full national coverage, but back then it only included data from inpatient care. All the diagnoses have been coded using ICD and the 10th edition was introduced in 1997. Since 2001, the register has also had coverage from specialized outpatient healthcare. The NPR does not include any data from Swedish primary care.

Difficulty of studying PSE with prospective studies

Several prospective studies have been made to follow the effects of treatment for PSE. Consoli et al. prospectively evaluated 106 patients treated for PSE over the span of a year with 3 visits for EEG and neurophysiological examination to assess the response [39], whereas the prospective study from Kutlu et al. followed 34 patients treated for PSE for a year with 5 outpatient visits [51].
Both of these studies have shown surprisingly effective responses to treatment compared to larger retrospective studies from healthcare, such as Stephen et al. who retrospectively followed the ASM response for 550 patients with PSE [42].

The advantages of retrospective studies to follow PSE is that it can follow the patients over many years, whereas the existing prospective studies have only followed patients for a short amount of time. Treatment for PSE usually spans over many years, and it is therefore important to evaluate the effectiveness over long periods of time. Another advantage of retrospective studies is that it can include a larger cohort, which can be a limiting factor for prospective studies.

Variation of the positive predictive value

A study published in 2011 by Ludvigsson et al. has validated many diagnoses in the Swedish IPR. It reviewed 132 papers to analyse the positive predictive value (PPV) of many different diagnoses and found the overall PPV to be about 85-95%, but there was a large variation

depending on the diagnosis, and the validation spanned from as low as 35% to as high as 100% [52].

2. Aim of the study

This study aimed to examine if common register-based criteria for PSE and crude register-based treatment algorithms corresponded with the information that existed in the patient medical records.

3. Materials and Methods

Study design and study cohort

This was a retrospective cohort study. The Swedish National Board of Health and Welfare identified 500 deceased individuals at random that fulfiled register-based criteria for PSE. Search criteria were: age above 18 years, an inpatient main diagnosis of acute ischemic stroke and/or intracerebral haemorrhage (ICD-10: I61, I63) during 2005-2010 and a subsequently seizure-related diagnosis (ICD-10: G40, G41, and R56.8, ICD-9: 345 and 780C) at least 7 days after the stroke diagnosis. The exclusion criterion was any seizure-related diagnosis before stroke.

A total of 328 medical records were received. This thesis was based on the first reviewed 177 medical records.

Data collection

Medical records from health care providers with seizure- or stroke-related register entries were ordered. Each record was reviewed in paper format and data were extracted to a pre-specified protocol detailing confirmation of stroke, confirmation of seizure, whether the patient had experienced ASS, eventual ASM treatment, and cause of seizures as assessed by the treating physician.

Statistical analyses

Positive predictive value, meaning the ratio of patients who actually had PSE to the total number of patients, was calculated as a ratio between the number of patients who were found to have a likely or definite epilepsy diagnosis after stroke to the total number of patients in the study. The confidence interval for the PPV was calculated using SPSS. All the data that were gathered when reviewing the patient journals was analysed using SPSS.

Student's contributions

I contributed to this research by analysing almost all the 177 patient journals by myself, doing all the data collection for each patient by carefully reading their medical records and filling out designed protocols to get as much information as possible from each patient with regards to PSE. This was overseen by my supervisors whom I could ask for help to ensure that everything was done in accordance with the project's goal. The data analysis was done in SPSS with the help of my supervisors.

Ethical approval

An application was sent to the Swedish Ethical Review Authority for an ethics review. The Authority did not have any ethical objections and the application was approved 2020-04-28.

Ethical discussion

All of the patients included in this study are deceased; thus there is no risk for physical or psychological injuries. None of the included patients were children under the age of 18. There are some philosophical arguments to consider, such as the respect for personal integrity even after death, and we have tried to take this into consideration by treating all the received information as sensitive personal data; from the gathered data, a file was be created with data from patients who have been unidentified by allocating each patient to a number.
All data were handled in a pseudonymized fashion.

The code key and the received medical records were stored in a locked fireproof cabinet.

When the study was completed and all the collected patient journals had been analysed, all the medical records as well as the code key were destroyed.

4. Results

Demographics

We included 177 adults, and from this group a total of 169 patients were found to have confirmed stroke. The proportion of males (100, 56.5%) was slightly higher than females (77, 43.5%). In the group of the 169 patients who had a confirmed stroke incidence, the mean age was 77.21 (CI95% 75.82-78.6).

Validation of stroke

A total of 169 patients (95.5%) had a verifiable stroke. The most common type of stroke was infarction, making up a minimum total of 72.3% of strokes. In at least 11.9% of cases, the type of stroke was a haemorrhage. In 8 cases, large parts of the requested patient journals were missing; making it impossible to analyse. In some cases the type of stroke could not be determined (table 2).

Table 1: Total amount of patients, how accurate the stroke and epilepsy diagnoses were and how many journals were missing from the 177 patients.

Total patients	177
Correct stroke diagnosis	169 (95.5%)
Correct epilepsy diagnosis*	133 (75%)
Missing journal	8 (4.5%)

** = the total number who had experienced an unprovoked seizure more than 7 days after stroke, excluding patients with epilepsy prior to stroke*

Table 2: Types of stroke

Type	**Frequency**
Infarction	128 (72.3%)
Intracerebral hemorrhage	21 (11.9%)
Unclear subtype	20 (11.3%)
Total strokes	169

Validation of epilepsy

A total of 10 patients had epilepsy before the stroke, whereas a total of 14 patients were found to have no epilepsy. 128 had a certain epilepsy diagnosis after stroke whereas 5 had a likely epilepsy diagnosis based on symptoms and circumstances, giving a total of 133 (95%CI 0.69-0.82) likely or definite epilepsy cases after stroke (table 3).

Table 3: At least one epileptic seizure more than 7 days after stroke

Definite epilepsy after stroke	128
Probable epilepsy after stroke	5
No epilepsy	14
Epilepsy before stroke	10
Total epilepsy cases	143

Regarding stated causes of epilepsy, stroke was the most common identifiable cause and accounted for 82.7% of causes (table 4).

Table 4: Probable cause of epilepsy as determined by the treating physician

Stroke	110 (82.7%)
Brain tumour	4 (3.0%)
Trauma	0 (0.0%)
Other	0 (0.0%)
Not stated	19 (14.0%)

Calculation of PPV

Calculations of PPV were performed for all patients and with the exclusion of those with missing records. Our study included a total of 177 patients but 8 of the patients had incomplete journals where large parts of the requested journal entries were missing, making it impossible to judge if the patient actually had stroke or epilepsy.
From the 177 total patients, 133 patients had epilepsy yielding a PPV of 75% - meaning 75% of the patients actually had received an epilepsy diagnosis after stroke. But if we calculate the proportion from only the patients who had complete records, the PPV is 79%.

Treatment

Out of the 133 patients with seizures, information concerning medical treatment was available in 119 patients. Of the 119 patients, 105 patients were prescribed ASM whereas 14 were not. Reasons stated for not wanting to prescribe ASM for the seizure were among others that the physician wanted to wait because of uncertainty of the diagnosis and did not want to initiate treatment in case the patient didn’t actually have epilepsy.

Table 5: Was the patient prescribed ASM for their epilepsy?

Yes	105 (79.0%)
No	14 (10.5%)

Can not be determined	14 (10.5%)

In table 6, the distribution of the most commonly used ASMs are shown. Carbamazepine was the most commonly prescribed first line treatment, making up a total of 33.8%. Valproate was prescribed first in 17.3% of cases, while Levetiracetam was the third most commonly prescribed at 13.5%. These three medications made up a total of 64.6% of all prescribed ASMs for epilepsy. In some patients, there was no data on which ASM was prescribed first.

Table 6: Which ASM was chosen as the first line of treatment?

Medication	**Frequency**
Carbamazepine	45 (33.8%)
Levetiracetam	18 (13.5%)
Phenytoin	3 (2.3%)
Gabapentin	2 (1.5%)
Valproate	23 (17.3%)
Lamotrigine	6 (4.5%)
Oxcarbazepine	3 (2.3%)
Phenobarbital	2 (1.5%)

5. Discussion

The objective of this study was to examine the accuracy of register-based criteria that are used to study PSE in the Swedish NPR. The clinical relevance of this is that if the investigated variables had a high validity, the same method could be used to identify large

patient cohorts for future studies with importance both for epidemiological knowledge and also for ASM treatment optimization.

Our results showed that epilepsy after stroke could be verified in 75% of our study population: meaning that from all the 177 patients who in their journals had received a stroke diagnosis and then a seizure-related diagnosis more than 7 days after the stroke, 133 actually fulfiled the criteria for epilepsy by having ≥1 unprovoked seizure more than 7 days after stroke. Sadly, in 8 patients large parts of the requested journals were missing, making it impossible to determine if the patient had PSE; if we exclude these cases, the PPV is 79%.

In comparison to our results, Ludvigsson et al. attempted to validate the Swedish IPR and found the average PPV to be 85-95% for the diagnoses they evaluated, but the results had a large variance and sometimes the PPV was as low as 35%. They did not analyse the PPV of epilepsy or stroke [52]. In comparison, a meta-analysis by Mbizvo et al. that calculated the PPV of an epilepsy diagnosis in administrative data, where the PPV ranged from 5.2%–100% (Canada), 32.7%–96.0% (USA), 47.0%–100% (UK), and 37.0%–88.0% (Norway), the results from our study were a high figure [53].

As discussed in the introduction, misdiagnosis is relatively common in epilepsy. A review done in 2005 by two epilepsy specialists in the UK found the epilepsy diagnosis doubtful in 16.3% of cases [54]. A newer review done in 2017 regarding the misdiagnosis of epilepsy estimated the misdiagnosis rates to be in the region of 20% [55]. Taking this into consideration, a PPV of 75-79% is quite high since these patients have fulfiled the ILAE criteria for PSE and considering the misdiagnosis rates, the PPV will never reach 100% since some of the patients will have received an epileptic diagnosis incorrectly.
A similar study to ours by Christensen et al. validated the epilepsy diagnosis in the Danish National Hospital Register [56]. They reviewed the medical records of 188 patients who had received an epilepsy diagnosis and could confirm it in 153 cases, yielding a PPV of 81%. However, this only validated epilepsy and not PSE, which is likely more complex to identify in medical records since it requires both a stroke diagnosis and then a subsequent unprovoked seizure without having received an epilepsy diagnosis beforehand; a total of 10 patients in our study had actually already received an epilepsy diagnosis before the stroke incident.

The results also provide interesting insights into the caveats of epilepsy management and its reflection of PSE. Some patients had ASS which was incorrectly diagnosed as epilepsy despite not fulfiling the diagnostic criteria. These patients were in some cases treated as PSE patients and received long-term epilepsy treatment. Other patients were noted to have received an epilepsy diagnosis in the patient records, but the diagnosis was later withdrawn because the symptoms mimicked something else (such as a new stroke). This diagnosis was still registered in the NPR. A few patients experienced another stroke with subsequent ASS, and the coding for that seizure led to the patient being included in this study despite not having an unprovoked seizure.

The patients who were selected for this study had strokes between 2005-2010. The NPR only started collecting data from outspecialized health care in 2001. Since then, awareness of PSE may have increased and it is possible that the PPV in our study would have increased if the patients had received the diagnosis more recently. The previously used definition of epilepsy was two or more unprovoked seizures [4], and ILAE first published the new practical definitions which included PSE in 2014 [12] which may have improved the diagnosis of PSE since there now exists a clear definition of when the diagnosis is warranted.

There are possible ways to increase specificity in studies of epilepsy in administrative data. One is to also require a prescription of an ASM [53]. In the meta analysis by Mbizvo et al., the authors found that including ASMs increased the amount of cases where patients actually had epilepsy, and in our population 105 out of 133 patients with PSE were prescribed ASM. A comprehensive study by Holden et al. that developed algorithms to detect epilepsy cases in administrative data examined several variables and found that the best model to identify epilepsy cases was to include either a pharmacy fill for an ASM or a CPT-4 code for ASM monitoring [57]. On the other hand, such a definition will miss more actual PSE cases by limiting the number of identified patients.

Another way of increasing PPV could be to only select patients with ICD-10 G40 (epilepsy). This would, however, increase reliance on physician awareness of the ILAE practical definition of epilepsy. In our material, more than 10% of patients with a first unprovoked

seizure were not diagnosed with PSE. If physicians wait for a second seizure, PSE rates using G40 in administrative data will be artificially low, because of the high mortality after stroke [58].

Because PSE should be diagnosed already after the first unprovoked seizure, register-based criteria includes all codes for seizures, thereamong ICD-10 R56.8 (Other and unspecified convulsions). This will pick up other causes like acute symptomatic seizures after stroke recurrence etc. Nonetheless, we round the PPV of a PSE definition including R56.8 to be 75%. Most epidemiological studies of PSE use one main definition, but also perform several sensitivity analyses using alternative definitions like including ASM or only counting G40 [53]. The results in our study support that practice.

We also collected data on ASM treatment. The most commonly prescribed first-line ASMs were Carbamazepine, Valproate and Levetiracetam, with all other ASMs being much less prescribed, which somewhat agrees with existing literature that has shown that these are among the most commonly prescribed ASMs for epilepsy [36, 37].

Methodological considerations

This study attempted to collect data that were evenly distributed from all the Swedish counties. A request for hospitals in each county was made but several counties did not provide any journal data for our study. This was considered to be a random effect, not influencing the results, but systematic bias is hard to exclude.
Furthermore, it was difficult to ascertain that complete medical records had been received. In some Swedish regions, electronic health records are dispersed over several providers, and we sometimes received only a subset of notes (discharge summary, etc). Nonetheless, our medical records review was conservative, so only cases where the records stated occurrence of a seizure, or such an occurrence could be reasonably inferred, were considered definite or probable cases, respectively. The high PPV is therefore still conservative, and could be improved yet.

Sadly, in a few cases, the journal data were scarce and it was difficult to make a clear determination of all the exact details from each patient visit. This may have been prevented if the medical records had instead been accessed electronically through the electronic journal systems in each county because then all the health care visits would have been available.

6. Conclusions and Implications

This study helps researchers in deciding whether to use register-based studies to identify and study PSE patients. Our study found that at least 75% of patients had a definite or likely epilepsy diagnosis after stroke, and several ways have been identified to possibly further improve the PPV, e.g. to require the prescription of an ASM, or to only select patients who had received an epileptic-related diagnosis (ICD-10; G40). Considering that the misdiagnosis rates of epilepsy are estimated to be in the regions of 10 to 20%, identifying at least 75% of PSE cases is high. Retrospective studies could therefore be considered an adequate way to study large groups of PSE patients in an effective and cost-effective way, but will likely always identify some patients who have not fulfiled the PSE criteria.

In summary, this degree project has validated register-based definitions of PSE. We had initially planned an investigation of all medical records, but received too large a sample to be reasonable to finish in a degree project. Therefore, this thesis constitutes an initial report, and further analyses of the data will be done in the research group.

Populärvetenskaplig sammanfattning

Identifiera poststroke epilepsi med hjälp av svenska nationella patientregister - en valideringsstudie

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Examensarbete: 30 hp
Program: Läkarprogrammet
År: 2021
Handledare: Johan Zelano
Nyckelord: Postapoplektisk epilepsi, nationella patientregister, antiepileptisk behandling,

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Epilepsi är en vanlig neurologisk åkomma som drabbar 1-3% av befolkningen och ungefär 70 miljoner världen över. Sjukdomen kan ge återkommande anfall som varierar i allvarlighet - det kan röra sig om allt från ofrivilliga muskelryckningar i olika delar av kroppen som varar i flera minuter till lätta ryckningar eller medvetandestörning över några sekunder där man ter sig frånvarande. Anfallen kan orsakas av skador eller sjukdomar i hjärnan, bland annat hjärntumörer och medfödda sjukdomar. Den vanligaste orsaken till epilepsi är dock stroke som står för 14-21% av epilepsifallen. Stroke är ett samlingsnamn för de sjukdomar som orsakar syrebrist till delar av hjärnan, antingen via en blodpropp eller blödning. En kort tid efter stroke, ungefär upp till en vecka, kan man ha så kallade provocerade anfall som uppstår på grund av den svåra påfrestningen som hjärnan utsätts för. Dessa anfall kan vara lika de man får när man har epilepsi men dessa återkommer ej när hjärnan har återhämtat sig efter stroken.

I vanliga forskningsstudier har det varit svårt att följa patienter med epilepsi efter stroke, vanligen är denna gruppen äldre och har flera sjukdomar, och den läkemedelsbehandling som man kan få för epilepsi sträcker sig vanligen över flera år. Forskargrupper har tidigare i flera projekt visat att svenska patientregister kan ge unika möjligheter att följa väldigt stora patientgrupper över en lång tid, men för att veta hur säkra slutsatser man kan dra av registerstudier vore det värdefullt att veta hur korrekta diagnoskoderna faktiskt är. Patientregistret innehåller patientuppgifter från vårdtillfällen på bland annat sjukhus, och här registreras till exempel behandling, kirurgi och diagnos. Diagnoskoder är de sjukdomar och

symtom som läkaren sätter i patientens journal efter patientens besök hos läkare - till exempel om patienten har epilepsi kommer läkaren kunna använda det som diagnoskod efter dennes besök hos läkaren.

I denna studie har vi bett socialstyrelsen att identifiera 177 avlidna patienter som i sin patientjournal, i samband med besök hos sjukvården, blivit diagnostiserad av läkare med först stroke och sedan, efter minst 7 dagar, krampanfall. Målet med studien har varit att gå igenom informationen i journalerna och undersöka hur korrekta diagnoskoderna. Hade patienten verkligen epilepsi efter stroke?
Resultaten i vår studie visade att 133 (75%) av de 177 patienterna faktiskt hade epileptiska anfall efter sin stroke. I vår studie inkluderade vi inte bara patienter med diagnoser för epileptiska anfall utan även anfall som kan ha varit orsakat av något annat - såsom ett provocerat anfall efter en till stroke. Eventuellt hade vi kunnat identifiera en ännu större andel patienter med epilepsi efter stroke om vi valde att endast välja de som blivit diagnostiserade med epilepsi.
Vi bedömer att patientregister kan användas som en kostnadseffektiv metod för att studera och få mer kunskap om epilepsi efter stroke, men att det alltid kommer inkluderas en viss andel patienter som ej har diagnosen. Denna andel kan dock minimeras om man använder rätt sökkriterier för att identifiera patienterna.

Acknowledgements

I would like to thank Johan Zelano, my main supervisor, for all the help during this semester and the weekly feedbacks given to me. I really felt a part of his research group and it was really fun participating in the group activities and also all the group meetings.

I would also like to thank David Larsson, my second supervisor, for letting me be a part of this project and for helping me with the data analyses. Both of them were really engaging and it felt like they really cared about the project.

Finally, I would like to thank Judith Klecki for doing an incredible work with writing all the digital data from the protocols and for helping me with a lot of technical stuff at the department.

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