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Original Article

Epilepsy Surgery in Adult Stroke Survivors with New-Onset Drug-Resistant Epilepsy

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ABSTRACT: ***Background:*** Despite its effectiveness, surgery for drug-resistant epilepsy is underutilized. However, whether epilepsy surgery is also underutilized among patients with stroke-related drug-resistant epilepsy is unclear. Therefore, our objectives were to estimate the rates of epilepsy surgery assessment and receipt among patients with stroke-related drug-resistant epilepsy and to identify factors associated with these outcomes. ***Methods:*** We used linked health administrative databases to conduct a population-based retrospective cohort study of adult Ontario, Canada residents discharged from an Ontario acute care institution following the treatment of a stroke between January 1, 1997, and December 31, 2020, without prior evidence of seizures. We excluded patients who did not subsequently develop drug-resistant epilepsy and those with other epilepsy risk factors. We estimated the rates of epilepsy surgery assessment and receipt by March 31, 2021. We planned to use Fine-Gray subdistribution hazard models to identify covariates independently associated with our outcomes, controlling for the competing risk of death. ***Results:*** We identified 265,081 patients who survived until discharge following inpatient stroke treatment, 1,902 (0.7%) of whom subsequently developed drug-resistant epilepsy (805 women; mean age: 67.0 ± 13.1 years). Fewer than six (≤0.3%) of these patients were assessed for or received epilepsy surgery before the end of follow-up (≤55.5 per 100,000 person-years). Given that few outcomes were identified, we could not proceed with the multivariable analyses. ***Conclusions:*** Patients with stroke-related drug-resistant epilepsy are infrequently considered for epilepsy surgery that could reduce morbidity and mortality.

RÉSUMÉ : Chirurgie de l'épilepsie chez des adultes ayant survécu à un AVC et souffrant d'épilepsie réfractaire récente. ***Contexte :*** Malgré son efficacité, la chirurgie pour l'épilepsie réfractaire demeure sous-utilisée. Cela dit, on ignore encore si la chirurgie de l'épilepsie est également sous-utilisée chez les patients souffrant d'épilepsie réfractaire liée à un AVC. Nos objectifs ont donc été d'estimer les taux d'évaluation et d'obtention d'une chirurgie de l'épilepsie chez les patients souffrant d'épilepsie réfractaire liée à un AVC et d'identifier les facteurs associés à ces résultats. ***Méthodes :*** Pour ce faire, nous avons utilisé des bases de données administratives du secteur de la santé pour effectuer une étude de cohorte rétrospective basée sur des résidents adultes de l'Ontario (Canada) qui ont obtenu leur congé d'un établissement de soins aigus après le traitement d'un AVC, et ce, entre le 1er janvier 1997 et le 31 décembre 2020. À noter qu'il ne devait pas exister de preuves préalables de crises épileptiques chez ces patients. De plus, nous avons exclu les patients qui n'ont pas développé par la suite une épilepsie réfractaire et ceux présentant d'autres facteurs de risque d'épilepsie. Nous avons également estimé les taux d'évaluation et d'obtention d'une chirurgie de l'épilepsie au 31 mars 2021. Enfin, nous avons prévu d'utiliser des modèles de Fine et Gray pour identifier les covariables indépendamment associées à nos résultats, contrôlant à cet égard le risque concurrent de décès. ***Résultats :*** Au total, nous avons identifié 265 081 patients qui ont survécu jusqu'à leur congé de l'hôpital après un traitement de l'AVC en milieu hospitalier, dont 1902 (0,7 %) qui ont ensuite développé une épilepsie réfractaire (805 femmes ; âge moyen : 67,0 ± 13,1 ans). Moins de six d'entre eux (≤ 0,3 %) ont été évalués pour l'obtention d'une chirurgie épileptique ou en ont bénéficiée avant la fin d'un suivi (≤ 55,5 pour 100 000 années-personnes). Étant donné que peu de cas ont ainsi été identifiés, nous n'avons pas pu procéder à des analyses multivariées. ***Conclusions :*** En définitive, les patients souffrant d'une épilepsie réfractaire liée à un AVC ne sont que rarement considérés pour une chirurgie de l'épilepsie, laquelle pourrait réduire les taux de morbidité et de mortalité.

Keywords: Medically intractable; Refractory; Epidemiology; Assessment; Receipt

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Introduction

An estimated 5.0% of stroke survivors develop new-onset epilepsy,[1] with younger individuals and those who had a hemorrhagic stroke, have a cortical lesion location or a larger lesion size experiencing even higher risk.[2] Patients who have seizures following their stroke experience worse outcomes than those who do not have seizures, with an increased risk of mortality at both 30 d and 1 year.[3] Fortunately, the risk of drug-resistant stroke-related epilepsy is lower than in focal epilepsy of other causes, estimated at 13%.[4] However, those whose seizures remain uncontrolled experience impaired quality of life[5] and an increased risk of mortality.[6,7]

Epilepsy surgery has been shown to increase the likelihood of seizure freedom and improve quality of life in patients with drug-resistant epilepsy.[8,9] Thus, it is now recommended that patients be considered for resective epilepsy surgery upon diagnosis with drug-resistant focal epilepsy.[9] However, rates of receipt remain low in Ontario, estimated at less than 2%.[10] Further, it is not clear if heterogeneity exists in the rate of epilepsy surgery utilization as a function of etiology. Thus, our objective was to estimate the rate of epilepsy surgery and assessment for epilepsy surgery candidacy among patients who have new-onset stroke-related drug-resistant epilepsy.

Materials and Methods

Study Design and Data Sources

We used data routinely collected for the administration of Ontario, Canada's publicly funded healthcare system to conduct a population-based, retrospective cohort study. With an estimated 14.2 million residents in 2017, Ontario is Canada's most populous province.[11] The data sets used include the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), CIHI Same Day Surgery Database (SDS), Ontario Health Insurance Plan (OHIP), Ontario Drug Benefit Claims (ODB), National Ambulatory Care Reporting System (NACRS), Ontario Census Area Profiles (CENSUS), Registered Persons Database (RPDB), Drug List (DIN), Ontario Hypertension Dataset (HYPER), Ontario Diabetes Dataset (ODD), Ontario Marginalization Index (ONMARG), Ontario Cancer Registry (OCR), and Immigration, Refugees and Citizenship Canada's (IRCC) Permanent Resident Database. These data sets were linked using unique encoded identifiers and analyzed at ICES.

The ODB contains data on publicly funded prescription medications dispensed in Ontario. Residents 65 years or older, 24 years and younger without private insurance coverage (as of January 1, 2018), those receiving social assistance, living in a long-term care facility or home for special care, receiving publicly funded home care, and those who have high drug costs and are enrolled in the Trillium Drug Program are eligible for coverage under the Ontario Drug Benefit program.[12] A full description of the ODB and the other data sets used in this analysis can be found in Table e-1 in the online supplementary material.

Study Population

We identified patients in the DAD who were treated in an Ontario acute care institution for a stroke during the accrual period, January 1, 1997, to December 31, 2020. Eligible strokes were identified using ICD-9 and ICD-10 codes for cerebral ischemia, intracerebral hemorrhage, and vertebro-basilar, carotid, and precerebral artery syndromes. We restricted our analysis to the patients' first stroke during the accrual period. After data cleaning exclusions, patients under 18 years of age or older than 105 years were excluded. We then limited our cohort to those who had an admission date for their stroke no earlier than July 1, 1996, to ensure that we could identify the remaining exclusion criteria, as OHIP data is only available as of July 1, 1991. We then excluded those who had a stroke within the 5 years before their cohort entry stroke, as we were interested in patients who developed epilepsy following their first stroke. We then excluded those who received healthcare for epilepsy, seizures, or brain surgery or were dispensed an antiseizure medication in the 5 years prior to hospital admission for their stroke. We restricted our analysis to individuals who had at least one seizure between hospital discharge following treatment of their stroke and December 31, 2020.

We restricted our cohort to patients who subsequently developed drug-resistant epilepsy by excluding patients who, between their first seizure following discharge for their stroke and December 31, 2020, were not dispensed at least two unique antiseizure medications (each with at least 90 d of consecutive use) followed by either a third unique antiseizure medication or a seizure. An antiseizure medication and generic versions of that medication were considered a single unique antiseizure medication. The date that the third antiseizure medication was dispensed or the seizure occurred was used as the date of drug-resistant epilepsy diagnosis.

We further excluded patients who had a brain tumor, cancer, central nervous system (CNS) infection, or traumatic or mild traumatic brain injury (TBI and mTBI, respectively) between the 5 years prior to hospital admission for their stroke and the date of drug-resistant epilepsy diagnosis, as patients with these conditions have an elevated risk of epilepsy for reasons other than their stroke.[13–17] A flow diagram depicting our cohort build can be found in Figure 1, and a complete list of the ICD-9, ICD-10, and OHIP codes used to define our inclusion and exclusion criteria can be found in Table e-2 of the online supplementary material.

Variable Definitions

Patient Characteristics

We measured several sociodemographic characteristics at the date of diagnosis of drug-resistant epilepsy, including age, sex, neighborhood household income quintile, neighborhood marginalization index factor scores, rurality, and immigration status. We also collected data on the receipt of electroencephalography (EEG) and magnetic resonance imaging (MRI) between patients' stroke discharge date and their diagnosis of drug-resistant epilepsy to determine if patients' epilepsy were adequately assessed according to current guidelines.[18] We also included the number of hospital encounters for seizures or status epilepticus identified between patients' first seizure following their stroke discharge and their drug-resistant epilepsy diagnosis.

Finally, we measured the Charlson comorbidity index and several specific comorbidities in the 2 years prior to patients' drug-resistant epilepsy diagnosis date, including diabetes, hypertension, atrial fibrillation, bipolar disorder or schizophrenia, and depression or anxiety. We also identified healthcare related to fractures in the 2 years prior to the drug-resistant epilepsy diagnosis. The specific codes used to identify these covariates are listed in Table e-2 of the online supplementary material.

Outcome

We followed the cohort from their drug-resistant epilepsy diagnosis date until March 31, 2021, death or receipt of the outcome. Our

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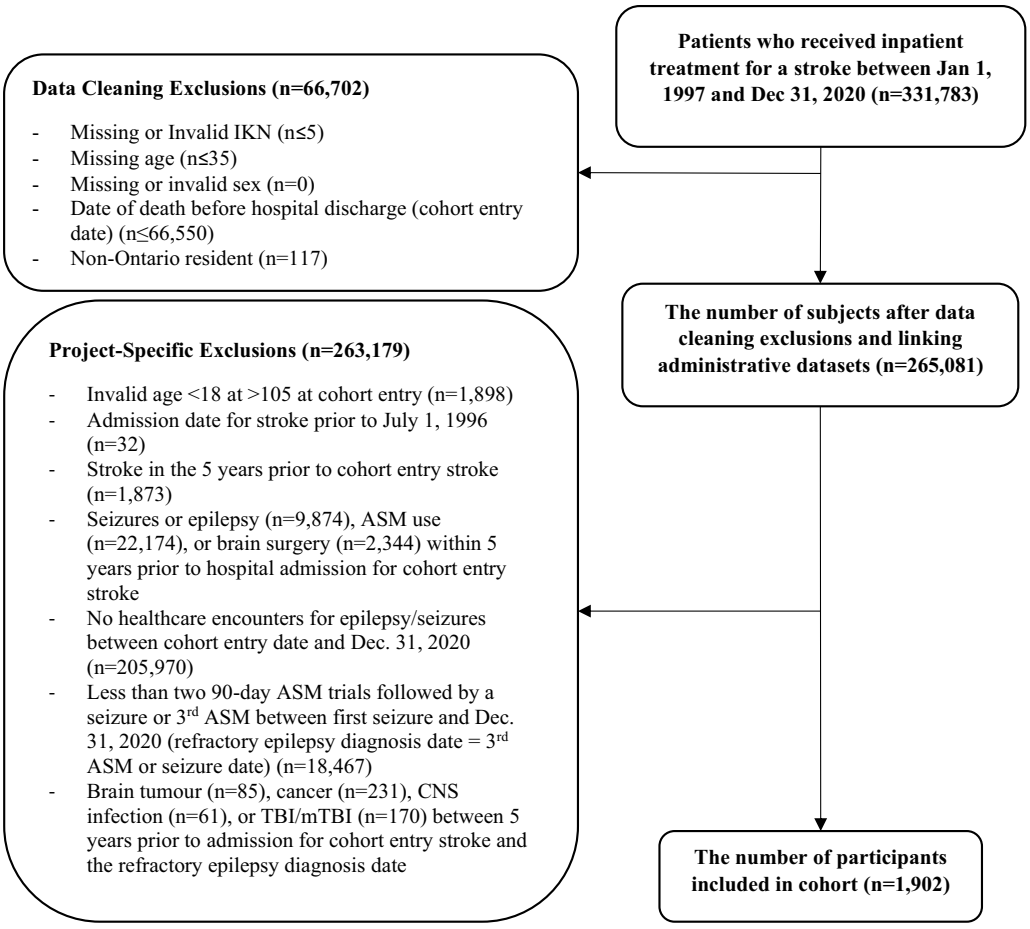

Figure 1: Flow diagram depicting the cohort build.
Note: ASM = anti-seizure medication, CNS = central nervous system, IKN = ICES key number, TBI/mTBI = traumatic brain injury/mild traumatic brain injury.

primary outcome, receipt of epilepsy surgery, was defined as the presence of any record in the OHIP database with an OHIP billing code for epilepsy surgery, including lobectomy, hemispherectomy, commissurotomy, and implantation of deep brain or vagus nerve stimulators. Our secondary outcome, assessment for epilepsy surgery candidacy, was defined as the first of:

i. the receipt of video telemetry, indicated by the simultaneous OHIP billing of four EEG-related codes, in patients who had an MRI between their drug-resistant epilepsy diagnosis and up to 14 d following the date of video telemetry,
ii. the date of OHIP billing for intracranial (surface or depth) electrodes, and
iii. the receipt of epilepsy surgery.

In Ontario, physicians must bill OHIP using all four of the EEG-related codes to receive compensation. The codes used to define these concepts are listed in Table e-2 of the online supplementary material.

Statistical Analysis

We estimated the rates of both assessment for epilepsy surgery candidacy and epilepsy surgery receipt by March 31, 2021. We planned to use *t*-tests to test for mean differences, Kruskal–Wallis tests for differences in medians, and Chi-square tests for differences in proportions between outcome groups in bivariate analyses. We also planned to use Fine-Gray subdistribution hazard models to identify factors associated with each of our outcomes in multivariable analysis. All analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC).

Ethical Standards

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require individual patient consent, nor review by a Research Ethics Board.

Data Sharing and Data Accessibility

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Role of the Funding Sources

The sponsors of this study had no role in study design; the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Table 1: Characteristics of study sample ($n = 1,902$)

Demographics	
Age, N (%)	
Mean (SD)	67.0 (13.1)
Median (IQR)	68 (60–76)
18–24	6 (0.3)
25–34	39 (2.1)
35–44	77 (4.0)
45–54	170 (8.9)
55–64	344 (18.1)
65–74	715 (37.6)
75–84	415 (21.8)
85–94	128 (6.7)
95+	8 (0.4)
Female, N (%)	805 (42.3)
Neighborhood Household Income Quintile, N (%)	
Quintile 1 (lowest)	459 (24.1)
Quintile 2	411 (21.6)
Quintile 3	370 (19.5)
Quintile 4	339 (17.8)
Quintile 5 (highest)	315 (16.6)
Missing	8 (0.4)
Immigrant, N (%)	187 (9.8)
Epilepsy Characteristics	
Number of hospital encounters for seizures/SE[a]	
Mean (SD)	1.1 (1.7)
Median (IQR)	1 (0–2)
Received an EEG, N(%)[b]	1,143 (60.1)
Received an MRI, N(%)[b]	843 (44.3)
Comorbidities[c]	
Charlson Comorbidity Index, N(%)	
0	287 (15.1)
1	328 (17.2)
2	192 (10.1)
≥ 3	650 (34.2)
No hospitalizations	445 (23.4)
Depression and anxiety, N (%)	872 (45.8)
Bipolar disorder and schizophrenia, N (%)	36 (1.9)
Diabetes, N (%)	787 (41.4)
Hypertension, N (%)	1,608 (84.5)
Atrial fibrillation, N (%)	324 (17.0)
Fractures, N (%)	117 (6.2)

Note: Parts of this table have been abbreviated. The full table (Table e-3) is available in the online supplementary material.
[a]Between the first seizure following stroke and drug-resistant epilepsy diagnosis.
[b]Between stroke and drug-resistant epilepsy diagnosis.
[c]In the 2 years prior to drug-resistant epilepsy diagnosis.

Results

We identified 331,783 patients who received inpatient treatment for an eligible stroke during the accrual period, 66,702 of whom were excluded due to missing health card numbers, demographic data, death during their hospital stay, or non-Ontario residency (Figure 1). We then excluded patients younger than 18 or older than 105 ($n = 1,898$), those who had a hospital admission date prior to July 1, 1996 ($n = 32$), and those who had a previous stroke ($n = 1,873$), seizures or epilepsy ($n = 9,874$), antiseizure medication use ($n = 22,174$), or brain surgery ($n = 2,344$) within the 5 years prior to hospital admission for treatment of their stroke. Patients who did not have a healthcare encounter for seizures or epilepsy following their hospital discharge ($n = 205,970$) and those who did not subsequently meet the definition of drug-resistant epilepsy ($n = 18,467$) were then excluded. Finally, we excluded patients who had a brain tumor ($n = 85$), cancer ($n = 231$), CNS infection ($n = 61$), or TBI or mTBI ($n = 170$) between the 5 years prior to patients' hospital admission for stroke treatment and their drug-resistant epilepsy diagnosis date. The final cohort consisted of 1,902 patients with drug-resistant stroke-related epilepsy, 805 (42.3%) of whom were women and had a mean age of 67.0 (SD = 13.1).

Five or fewer participants were assessed for epilepsy surgery candidacy (≤55.5 per 100,000 person-years), and five or fewer participants received epilepsy surgery (≤55.5 per 100,000 person-years) by the end of follow-up. We have not reported the precise number or rate of our outcomes because small values (≤5) used to describe our cohort must be suppressed to protect patient privacy. The median follow-up durations to estimate the rates of epilepsy surgery assessment and receipt were both 3.6 (IQR = 1.5–7.0) years. There were 895 (47.1%) deaths over follow-up. Given the small number of events observed, we could not proceed with the planned bivariate and multivariable analyses for either outcome. However, the distribution of covariates for the entire cohort is presented in Table 1.

Discussion

In this study, we found that ≤0.3% of patients with stroke-related drug-resistant epilepsy were assessed for or received epilepsy surgery by the end of follow-up. Although the exact rates of these outcomes cannot be reported, we can observe that these outcomes are very infrequent in this population. These results indicate that assessment for epilepsy surgery candidacy and its receipt may be even lower than the previously estimated rates of these outcomes among those with drug-resistant epilepsy of any etiology in Ontario.[10]

Epilepsy surgery has been shown to reduce the frequency of seizures and improve quality of life.[8,9] Although sparse, there also exists some evidence that surgery is effective in those with drug-resistant epilepsy of stroke-related etiology. Marchi et al.[19] found that in 12 patients with stroke-related drug-resistant epilepsy of any age who received surgery, all had a surgical outcome of at least Engel Class III, with two-thirds achieving complete seizure freedom (Engel Class IA). In another study of children with stroke-related drug-resistant epilepsy, 10 of 12 patients had an Engel Class I outcome.[20] Similarly, in a case series reported by Ghatan et al.,[21] all 19 patients who received surgery for drug-resistant

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epilepsy due to perinatal stroke achieved seizure control of Engel Class I. They further reported significant long-term improvements in disability, cognitive development, and quality of life.[21]

Approximately two-thirds of our cohort was composed of patients 65 years and older (66.6%). Epilepsy presents somewhat differently in this age group relative to younger patients, with older patients having longer periods of post-ictal confusion and experiencing status epilepticus more frequently.[22] Further, the treatment of epilepsy in this population can be challenging due to potential medication interactions, a high frequency of adverse events at lower doses and serum concentrations than in younger patients, and the high risk of osteoporosis in older women.[22] Given the challenges of medically treating epilepsy in older adults, surgical remediation offers an opportunity to reduce epilepsy-related morbidity and mortality in this age group.

We could not identify any studies that examined the efficacy of epilepsy surgery specifically in an older adult stroke-related epilepsy population. However, Sen et al.[23] have summarized the state of the literature regarding the efficacy of surgery for the treatment of drug-resistant epilepsy in older adults. Sen et al.[23] caution that additional high-quality research is necessary to inform the treatment of older adults with surgery but conclude that the existing research indicates that resective epilepsy surgery is safe and effective in appropriately chosen older patients. Thus, the existing literature suggests that both younger and older adults with stroke-related drug-resistant epilepsy should at least be assessed for epilepsy surgery candidacy.

The collective findings of low rates of assessment for epilepsy surgery and its receipt despite its apparent benefits indicate the existence of barriers to this treatment. Barriers to being assessed for epilepsy surgery candidacy include physician and patient beliefs about risks and benefits and insufficient infrastructure to assess all patients with drug-resistant epilepsy.[10] A sample of neurologists in the USA reported being less likely to refer patients for surgical evaluation due to older age.[24] A similar study conducted in Canada found that 48.6% of surveyed neurologists lack an understanding of the definition of drug-resistant epilepsy and have other misconceptions about the features of epilepsy that would preclude a patient from receiving epilepsy surgery.[25] Patient or guardian apprehension was reported as the main barrier to epilepsy surgery by 10.5% and inadequate health care resources by over 75% of the surveyed neurologists.[25]

The main limitation of this study was in our use of administrative health data. These data are not collected for research purposes, which has important implications for the accuracy of our concept definitions. This limitation is of particular relevance to our cohort build.

When identifying patients with a first clinical stroke during our accrual period, some eligible patients may not have been captured, and some included patients may not have had an eligible stroke. To identify patients with eligible strokes before April 1, 2002, we used ICD-9 codes for which the positive predictive values (PPVs) are known to be high in the DAD,[26] the inpatient database used in the present study. Between April 1, 2002, and the end of the accrual period, we used ICD-10 codes validated by Porter et al.[27] to identify intracerebral hemorrhage, ischemic stroke, and transient ischemic attacks (TIAs), all with PPVs of 78.8% or higher. However, because these codes were not validated for the identification of patients at risk of stroke-related epilepsy, we excluded codes that represented conditions that do not increase epilepsy risk. Specifically, we excluded TIA codes G45.3 (amaurosis fugax), G45.8 (other transient cerebral ischemic attacks and related syndromes), and G45.9 (transient cerebral ischemic attack, unspecified), and ischemic stroke code H34.1 (central retinal artery occlusion). Therefore, the precise PPVs of the ICD-10 codes used to identify patients at risk of stroke-related epilepsy are unknown.

We then excluded patients who did not develop epilepsy following their stroke. Although a validated definition of epilepsy for use in administrative health data is available for our region,[28] we opted to use a more liberal definition requiring a single seizure following the stroke. This definition was selected to better reflect the epilepsy diagnostic process in patients with a history of stroke, as all are at increased risk of additional seizures given a single unprovoked seizure. We expect that this definition is sufficiently specific, considering that we subsequently applied exclusions to define drug-resistant epilepsy.

We then excluded patients who did not develop drug-resistant epilepsy. Residents 65 years and older, 24 years and younger without private insurance coverage (as of January 1, 2018), those in receipt of certain financial assistance programs, and several other select groups are eligible for coverage by the ODB program. Considering that stroke risk increases with age,[29] we likely captured most patients with drug-resistant epilepsy following a first clinical stroke. However, some eligible younger adults were likely excluded, as the ODB program does not cover all members of this population. Therefore, we likely underestimated the rates of epilepsy surgery assessment and receipt in our region.

We caution that our results may only be generalizable to those with drug-resistant epilepsy following a clinical stroke rather than that which follows a sub-clinical stroke and may have limited generalizability to regions with dissimilar infrastructure for the treatment of epilepsy or with different healthcare systems more generally. However, we believe that our findings are likely to be generalizable at least to the USA, considering that previous research in that region has also estimated low rates of epilepsy surgery receipt as has been estimated in Ontario.[10,30]

In this study, we found that patients with stroke-related drug-resistant epilepsy are rarely assessed for a procedure that could improve their quality of life and reduce the excess risk of mortality associated with epilepsy. There are likely misconceptions held by both patients and neurologists about the safety and efficacy of epilepsy surgery, particularly in older adults and patients with stroke-related epilepsy. Finally, the lack of sufficient infrastructure to assess all patients with drug-resistant epilepsy may also be responsible for the underutilization of surgery in this patient population. Given the lack of evidence indicating that patients with stroke-related drug-resistant epilepsy are typically ineligible for epilepsy surgery, these patients should at least be assessed for surgical candidacy.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.300.

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Conflict of Interest. T Antaya, B Le, L Richard, A Qureshi, and S Shariff report no conflicts of interest. L Sposato has received speaker honoraria from Pfizer

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Statement of authorship. TA: literature search, project planning, data interpretation, manuscript writing; BL: data analysis, data interpretation, project planning, manuscript editing; LR: data analysis, data interpretation, manuscript editing; AQ: project planning, manuscript editing; SS: study design, data analysis oversight, manuscript editing; LS: project planning, manuscript editing; and JB: project oversight, study design, data interpretation, manuscript editing.

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