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Medicare claims can identify post-stroke epilepsy

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ABSTRACT

Objective: There have been no validated Medicare claims-based algorithms available to identify epilepsy by discrete etiology of stroke (e.g., post-stroke epilepsy, PSE) in community-dwelling elderly individuals, despite the increasing availability of large datasets. Our objective was to validate algorithms that detect which patients have true PSE.

Methods: We linked electronic health records (EHR) to Medicare claims from a Medicare Pioneer Accountable Care Organization (ACO) to identify PSE. A neurologist reviewed 01/2012-12/2014 EHR data from a stratified sample of Medicare patients aged 65+ years to adjudicate a reference-standard to develop an algorithm for identifying patients with PSE. Patient sampling strata included those with: A) epilepsy-related claims diagnosis (n = 534 [all]); B) no diagnosis but neurologist visit (n = 500 [randomly sampled from 4346]); C) all others (n = 500 [randomly sampled from 16,065]). We reconstructed the full sample using inverse probability sampling weights; then used half to derive algorithms and assess performance, and the remainder to confirm performance. We evaluated predictive performance across several measures, e.g., specificity, sensitivity, negative and positive predictive values (NPV, PPV). We selected our best performing algorithms based on the greatest specificity and sensitivity.

Results: Of 20,943 patients in the reconstructed sample, 13.6% of patients with epilepsy had reference-standard PSE diagnosis, which represents a 3-year overall prevalence of 0.28% or 28/10,000, and a prevalence within the subpopulation with stroke of 3%. The best algorithm included three conditions: (a) at least one cerebrovascular claim AND one epilepsy-specific anticonvulsant OR (b) at least one cerebrovascular claim AND one electroencephalography claim (specificity 100.0% [95% CI 99.9%–100.0%], NPV 98.8% [98.6%–99.0%], sensitivity 20.6% [95% CI 14.6%–27.9%], PPV 86.5% [95% CI 71.2%–95.5%]).

Conclusion: Medicare claims can identify elderly Medicare beneficiaries with PSE with high accuracy. Future epidemiological surveillance of epilepsy could incorporate similar algorithms to accurately identify epilepsy by varying etiologies.

1. Introduction

Ischemic brain insults (stroke) and epilepsy rank among the most prevalent and damaging neurological diseases in the elderly. Evidence points towards a complex and bidirectional nature. Those diagnosed with epilepsy have an increased risk for stroke (Cleary et al., 2004; Shinton et al., 1987; Wannamaker et al., 2015). Meanwhile, ischemic stroke increases the risk for epilepsy (Arboix et al., 1997; Bladin et al.,

Abbreviations: ACO, accountable care organization; AED, antiepileptic drug; AUROC, area under the receiver operating characteristic curve; EEG, electroencephalography; EHR, electronic health record; ICD-9, international classification of disease- ninth revision; ILAE, international league against epilepsy; NPV, negative predictive value; PPV, positive predictive value; PSE, post-stroke epilepsy

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2000; Burn et al., 1997; Kilpatrick et al., 1990; Kotila and Waltimo, 1992; Labovitz, 2001; Lancman et al., 1993; Merkler et al., 2018; So et al., 1996; Stefanidou et al., 2017). Prior studies suggest that stroke alone accounts for approximately 30–50% of all elderly-onset epilepsy (Hauser et al., 1996; Ramsay et al., 2004). As the United States population ages, the incidence and prevalence of both epilepsy and stroke are expected to rise substantially.

Several US studies have used algorithms based on administrative data to identify epilepsy (Faught et al., 2012; Holden et al., 2005) and stroke (Goldstein, 1998; Heckbert et al., 2004; Kumamaru et al., 2014; Tirschwell and Longstreth, 2002) patients. Existing algorithms for validation in electronic health records (EHRs) widely vary in the breadth and depth of their methods (e.g., varying definitions of late versus early onset epilepsy, varying sources of data, varying performance metrics), and most do not generalize across datasets or subpopulations (e.g., elderly versus young adults, community-dwelling versus institutionalized) (Moura et al., 2017).

Importantly, these algorithms have not been validated to identify discrete epilepsy etiologies (e.g., post-stroke epilepsy [PSE]) in the elderly for epidemiological research. As a result, current estimates of prevalent PSE in the elderly substantially vary in the existing literature (2.5%–9.7%) (Bladin et al., 2000; Burn et al., 1997; Lossius et al., 2005; Pitkänen et al., 2016; So et al., 1996). To improve our ability to better monitor care for this patient population, we developed and validated Medicare claims-based algorithms to detect PSE among community-dwelling elderly beneficiaries.

2. Methods

We conducted our study in four steps. First, we created a linked dataset containing individual-level data from claims and EHRs. Second, we determined PSE status through neurologist review of the EHRs on a stratified random subsample. The neurologist reviewing the clinical data determined disease status independent of the claims information. Third, we reviewed the literature and used expert knowledge to develop and test a series of algorithms using all claims available during a three-year period. Finally, we described the performance of the best performing algorithm (Lalkhen and McCluskey, 2008; Schwartz and Martin, 2012).

The study's protocols were approved by the Institutional Review Board of Massachusetts General Hospital, and informed consent was waived.

2.1. Patient population

We obtained patient data from EHRs of the Partners Healthcare System, a large integrated delivery system containing two major tertiary care hospitals, five community hospitals, 32 community health centers, and over 6000 physicians. Patient EHRs contain all medical records, including visit information, prescriptions, and laboratory values. EHR data were linked to Medicare claims data within the Partners Accountable Care Organization (ACO). For our study, we used Medicare Parts A, B, and D.

Our study window for reviewing EHR data and retrieving claims was 01/2012–12/2014. Within this three-year window, we identified Medicare beneficiaries aged 65 + years who were continuously enrolled in Medicare Parts A and B, had a Medicare original reason for entitlement (OREC) of age or disability, were a Medicare beneficiary over the entire three year study window, and were community-dwelling at the start of each calendar year (Yun et al., 2010). Using these limited criteria, we identified 20,943 eligible patients.

We then drew a stratified random sample of patients for review of EHRs (Fig. 1). We used claims coded under the International Classification of Disease, Ninth Revision (ICD-9) to create three strata. Stratum A consisted of all patients (n = 534) with at least one primary diagnosis suggestive of epilepsy (345.xx or 780.39). We then examined the remaining patients with no epilepsy claims and identified patients who were seen by a neurologist (stratum B, n = 4346) and patients who were not seen by a neurologist (stratum C, n = 16,065), taking a random sample of 500 patients from each. Our sampling approach yielded a sample of 1534 patients.

2.2. EHR review

A neurologist (LM) who was blinded to the patients' sampling strata adjudicated epilepsy and PSE diagnosis of patients within the EHR review sample. Within EHRs, the richest sources of information were inpatient physician documentation, ED documentation, and discharge documentation. To confirm epilepsy diagnosis based on International League Against Epilepsy (ILAE) definitions the neurologist utilized all available data within EHRs, which included physician notes and electroencephalography (EEG) and brain imaging data (Fisher et al., 2017; Scheffer et al., 2017). Next, the neurologist identified and confirmed etiology (e.g., focal dyscognitive seizures due to lesion, ischemic insult, hemorrhagic insult, mesial temporal sclerosis) among all patients with epilepsy. PSE, defined as epilepsy etiology of focal dyscognitive seizures due to ischemic insult (with or without secondary generalization), was confirmed only after: A) confirming an ischemic stroke event; B) confirming paroxysmal symptoms (i.e. unprovoked seizures) were not idiopathic or potentially related to other structural pathologies; and C) confirming, per the EHR, clinical consistency and that the epileptic events were preceded by the cerebrovascular event. We restricted our definition of PSE to "focal dyscognitive seizures due to ischemic insult" (i.e. excluded etiology of hemorrhagic stroke) for increased precision.

We created EHR-based variables of epilepsy diagnosis, seizure type and/or epilepsy etiology, seizure occurrence, focal seizure type, generalized seizure type, and differential diagnosis (Table B.1). Epilepsy diagnosis and seizure occurrence variables were binary. We similarly based the variables seizure type and/or epilepsy etiology (e.g., focal dyscognitive seizure due to ischemic brain insult), focal seizure type (e.g., tonic seizure with impaired awareness), and generalized seizure type (e.g., tonic-clonic) on current ILAE classification guidelines (Fisher et al., 2017; Scheffer et al., 2017). Next, we operationally defined PSE by the reference-standard epilepsy etiology of seizures due to ischemic brain insult (i.e., includes epilepsy in which etiology was most likely or definitely a prior ischemic stroke). We also captured the reason for a negative epilepsy diagnosis when there was suspicion of seizures (e.g., drug or alcohol withdrawal seizures, psychogenic non-epileptic seizures, singular provoked seizure).

We consulted practicing neurologists within the neurology department in instances of an unclear epilepsy diagnosis in the EHR. If a consensus for a definitive epilepsy diagnosis for a patient was not reached, then the patient was recorded as having an unclear diagnosis. There was a total of 16 patients with an unclear epilepsy diagnosis.

We additionally captured pertinent treatment information and created binary variables for antiepileptic drugs (AEDs), such as levetiracetam, lamotrigine, phenytoin, valproic acid, carbamazepine, gabapentin, and benzodiazepines.

2.3. Medicare claims-based variables

We created Medicare claims-based variables to describe our cohort and to construct our algorithms. First, we obtained basic demographic information on the age and sex of the sample from claims. Next, we assembled lists of relevant Medicare claims for epilepsy diagnosis, stroke diagnosis, procedures for EEG and brain imaging, place and provider services, and medications (Table B.2). We were blinded to both the patients' strata and the EHR based diagnoses in this step.

We used clinical knowledge to create four claims-based candidate variables for use in our algorithm: 1) epilepsy diagnosis; 2) stroke diagnosis; 3) EEG; and 4) specific AED (Table 1). "Epilepsy diagnosis" sums the number codes indicative of epilepsy as either a primary,

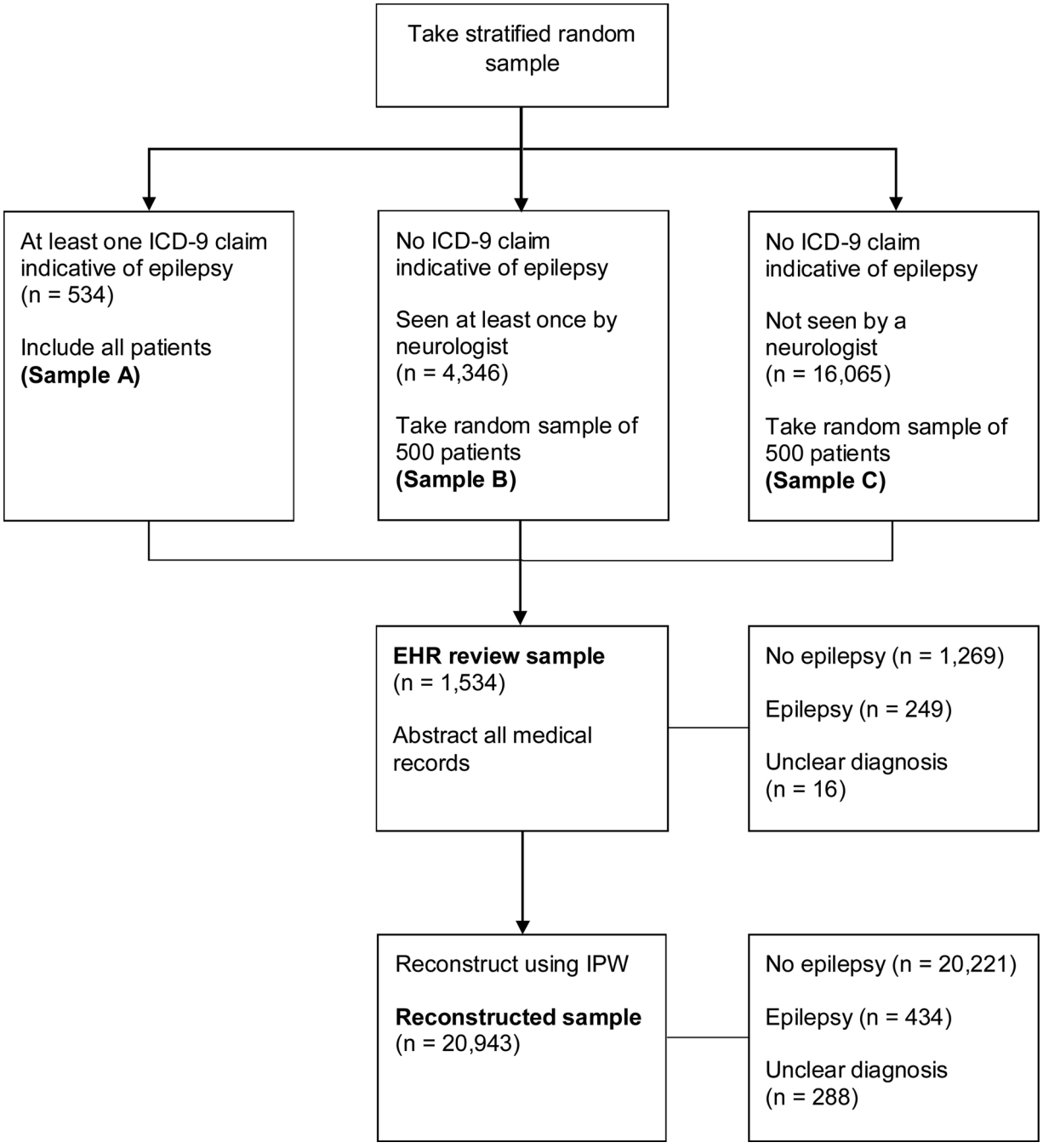

Fig. 1. Legend. Sampling strategy and reference-standard epilepsy diagnosis.
ICD-9, International Classification of Disease, Ninth Revision; IPW, inverse probability sampling weights.
Stratified random sampling of patients and adjudicated reference-standard epilepsy diagnosis.

Table 1
Variables constructed from claims.

Variable	Description
Epilepsy diagnosis	Integer; Claim indicative of epilepsy as primary, secondary, or tertiary diagnosis
Stroke diagnosis	Integer; Claims indicative of stroke as primary, secondary, or tertiary diagnosis
EEG	Integer; Claims indicative of EEG performed
Specific AED	Integer; Claims indicative of levetiracetam, lamotrigine, phenytoin, valproic acid, or carbamazepine

AED, antiepileptic drug; EEG, electroencephalography.
Description of claims-based variables.

Table 2
Reconstructed Sample Characteristics.

Characteristic	Reconstructed Sample (n = 20,943)
Demographics	
Age, Mean (SD)	75.9 (25.4)
Female, n (%)	12,348 (59.0)
Clinical[a]	
Non-confirmed epilepsy diagnosis, n (%)	20,221 (96.6)
Confirmed epilepsy diagnosis, n (%)	434 (2.1)
Unclear diagnosis, n (%)	288 (1.3)

Breakdown of reconstructed sample.
[a] Clinical characteristics based on review of electronic health records.

secondary, or tertiary diagnosis. “Stroke diagnosis” sums the number of cerebrovascular codes indicative of stroke. “EEG” additionally sums EEG procedure codes coinciding with an epilepsy code. Lastly, “specific AED” accounts for the presence of claims of either levetiracetam, lamotrigine, phenytoin, valproic acid, or carbamazepine (the most specific AEDs prescribed for patients with epilepsy).

We then reconstructed the initial sample using inverse probability sampling weights (IPW) and analyzed the claims-based clinical and treatment characteristics of the initial sample (i.e., we weighted our sample of 1534 patients to represent our initial sample of 20,943 patients; Table 2). We presented the distribution of our claims-based variables (Tables B.3 and B.4) and our reference-standard EHR-based PSE and epilepsy diagnoses (Table B.5).

2.4. Statistical analysis (algorithm development and validation)

We first divided the reconstructed sample into two subsets: 1) algorithm development (re-weighted n = 10,473) and 2) algorithm validation (re-weighted n = 10,559), and verified similar distributions of demographic and epilepsy diagnoses between the two subsets (Table B.6).

We then listed all possible combinations of our four claims-based variables and used expert knowledge to select seven candidate algorithms to generate an indicator variable for PSE. We evaluated the algorithms in the development subset and chose those with the highest performance metrics, and then validated these choices in the validation subset. Each patient was characterized as PSE/no PSE, given the parameters of the algorithm. For instance, algorithm A required the presence of at least one claim for stroke and either at least one specific AED or at least one EEG (Fig. 2, Table 3) for a person to be identified as having PSE.

To analyze the performance of each algorithm, we calculated sensitivity (percentage of patients correctly identified by the algorithm with PSE) and specificity (percentage of patients correctly identified by the algorithm with no PSE) of each algorithm. We then calculated the positive predictive value (percentage of all algorithm-identified patients with PSE that have true PSE) and the negative predictive value (percentage of all algorithm-identified patients with no PSE that have true no PSE).

When defining the “best” algorithm, we examined the tradeoff between sensitivity and specificity. If the criteria for a positive test result were stringent, then there would be fewer false positives, but a drop in sensitivity. Conversely, if the criteria were relaxed, then there would be fewer false negatives, but a drop in specificity. Overall, highly sensitive identification methods are generally developed for screening (e.g., studies of stroke incidence in which the criteria for diagnosing "stroke" are then relaxed to include all the possible results and may include several false positives). Conversely, our algorithm was developed to be used in epidemiological research (e.g., comparative effectiveness research with comparison of outcome rates in different populations). Here, a highly specific algorithm can allow for accurate estimations of rate ratios even without perfect sensitivity. In other scenarios, sensitivity might be more meaningful (e.g., estimations of prevalence of rare disease). Therefore, we defined the best performing algorithm as the one which maximized specificity and sensitivity (i.e. best is 100% specificity; among the 100% specific algorithms, choose the most sensitive) (Lalkhen and McCluskey, 2008; Schwartz and Martin, 2012).

To create and validate our algorithms, we used SAS® (SAS Institute, 2011). To visualize performance metrics (sensitivity, specificity, PPV, NPV, AUROC), we used STATA (StataCorp, 2015). For easy replicability and transparency, we the provide code used for each software package in Appendix A.

3. Results

3.1. Patient population

Of 20,943 patients in the reconstructed dataset, 59.0% (n = 12,356) were female. The average age was 75.9 years (SD = 25.4 years). 8.9% of all patients had at least one claim for stroke and 2.1% had PSE (EHR confirmed) (Table 2).

13.6% of patients with epilepsy had PSE, which represents a 3-year overall prevalence of 0.28% or 28/10,000, and a prevalence within the subpopulation with stroke of 3% (Table B.5). 288 patients lacked sufficient data to adjudicate an epilepsy diagnosis or identification. Only 74.6% of patients with PSE had at least one claim for stroke.

3.2. Algorithms

We developed seven algorithms to identify PSE as a diagnostic tool. Of those, three algorithms had a specificity of 100.0%. The best performing algorithm (algorithm A) had the highest specificity and sensitivity. It included “stroke diagnosis” and either “specific AED” or “EEG” (Table 3). Specificity was 100.0% (95% CI 99.9%–100.0%), sensitivity was 20.6% (95% CI 14.6%–27.9%), and NPV was 98.8% (95% CI 98.6%–99.0%) (Table 4; Data that guided calculations is provided in Tables B.7 and B.8). 151 patients were misclassified as having PSE by algorithm A (i.e., false positives), and 13 patients were misclassified as not having PSE (i.e., false negatives) (Tables B.9 and B.10, respectively). Of the false positives, levetiracetam was the most frequently prescribed AED (n = 17, 11.3%). Further interrogation of algorithm A, in which all AEDs were included, decreased specificity (99.9%; 95% CI 99.8%–99.9%), sensitivity (3.1%; 95% CI 1.5%–5.7%), and NPV (97.1%; 95% CI 96.7%–97.4%)

Algorithm B included “stroke diagnosis” and either “epilepsy diagnosis” or “specific AED” as variables (Table 3) and yielded similarly high specificity (100.0%, 95% CI 99.9%–100.0%) and NPV (95.9%, 95% CI 95.5%–96.3%) (Table 4). Algorithm C included all four variables (Table 3), and had a specificity of 100.0% (95% CI 99.9–100.0%) and NPV of 95.6% (95% CI 95.2%–96.0%) (Table 4).

Of note, algorithm D had the highest sensitivity, with confidence intervals that overlap with algorithm A (sensitivity of 46.8%, 95% CI 34.0%–59.9%) (Table 4). It included the variables “stroke diagnosis” and “specific AED” (Table 3). However, given the decrease in specificity (99.9%, 95% CI 99.8%–100.0%), we conservatively consider algorithm A as our best performing algorithm.

4. Discussion

Our study is the first to develop and validate Medicare claims-based algorithms that identify community-dwelling elderly beneficiaries with a discrete etiological classification of epilepsy (i.e., PSE). Our most accurate algorithm, which had high specificity, NPV, and PPV utilized variables that were indicative of cerebrovascular disease, epilepsy-specific AEDs, and EEG. Two similar algorithms, which incorporated claims indicative of cerebrovascular disease, epilepsy, EEG, and epilepsy-specific AEDs additionally demonstrated high-performance

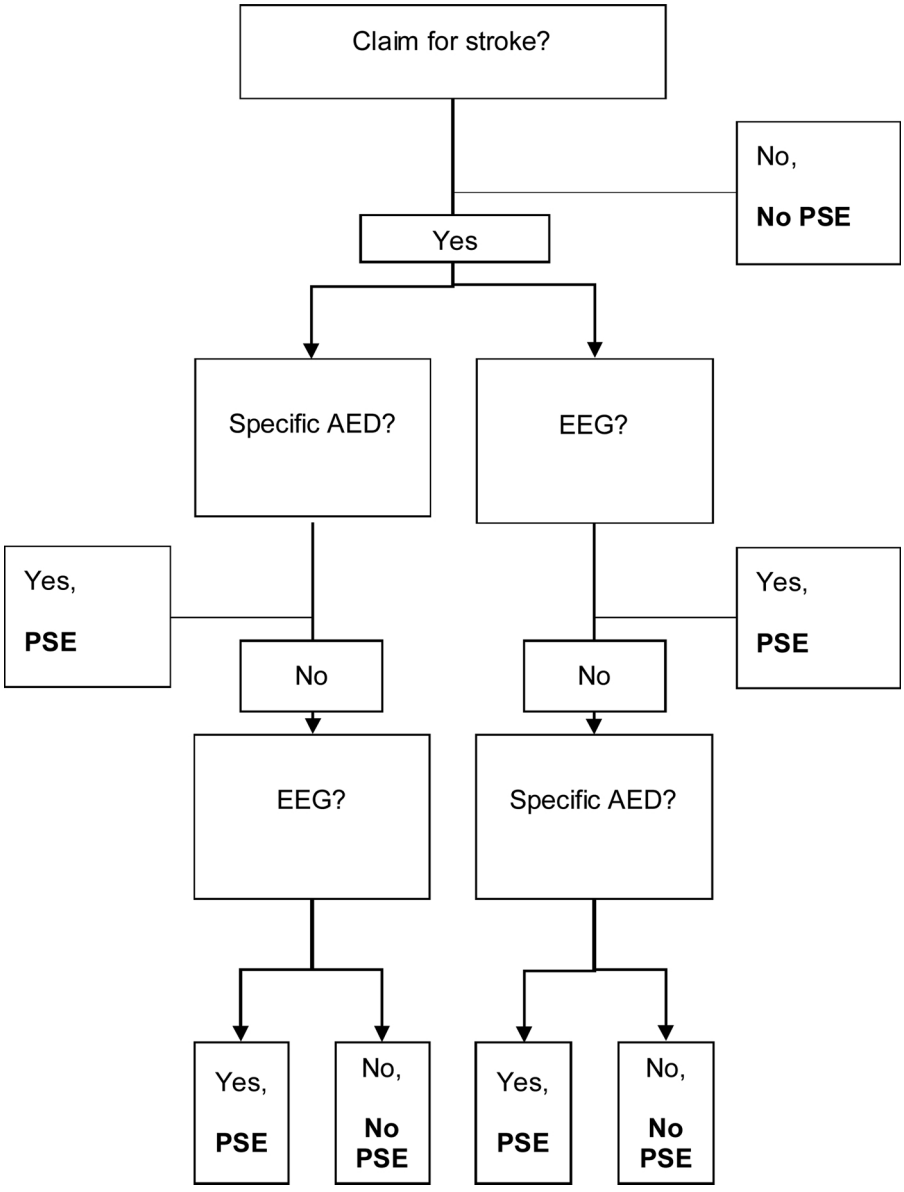

Fig. 2. Legend. Best performing algorithm.
AED, antiepileptic drug; EEG, electroencephalography PSE, post-stroke epilepsy.
Logic of best-performing algorithm (Algorithm A).

Table 3
Characteristics of claims-based algorithms.

Variable	Algorithm A[a]	Algorithm B[b]	Algorithm C[c]	Algorithm D[d]	Algorithm E[e]	Algorithm F[f]	Algorithm G[g]
Stroke diagnosis	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Epilepsy diagnosis	No	Yes	Yes	No	Yes	Yes	No
EEG	Yes	No	Yes	No	No	Yes	Yes
Specific AED	Yes	Yes	Yes	Yes	No	No	No

AED, antiepileptic drug; EEG, electroencephalography.
Claims-based variables used to construct the algorithms.
[a] Stroke diagnosis and EEG OR Stroke diagnosis and Specific AED.
[b] Stroke diagnosis and Epilepsy diagnosis OR Stroke diagnosis and Specific AED.
[c] Stroke diagnosis and Epilepsy diagnosis OR Stroke diagnosis and EEG OR Stroke diagnosis and Specific AED.
[d] Stroke diagnosis and Specific AED.
[e] Stroke diagnosis and Epilepsy diagnosis.
[f] Stroke diagnosis and Epilepsy diagnosis OR Stroke diagnosis and EEG.
[g] Stroke diagnosis and EEG.

Table 4
Results of Claims-based Algorithms.

Algorithm	Specificity % (95% CI)	Sensitivity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)	AUROC (95% CI)
Development Subset					
Algorithm A	100.0 (99.9-100.0)	20.6 (14.6-27.9)	98.8 (98.6-99.0)	86.5 (71.2-95.5)	0.60 (0.57-0.63)
Algorithm B	100.0 (99.9-100.0)	7.2 (5.0-9.9)	95.9 (95.5-96.3)	89.2 (74.6-97.0)	0.54 (0.52-0.55)
Algorithm C	100.0 (99.9-100.0)	6.8 (4.7-9.4)	95.6 (95.2-96.0)	89.2 (74.6-97.0)	0.53 (0.52-0.54)
Algorithm D	99.9 (99.8-100.0)	46.8 (34.0-59.9)	99.7 (99.6-99.8)	78.4 (61.8-90.2)	0.73 (0.67-0.80)
Algorithm E	99.9 (99.8-99.9)	5.4 (3.5-8.0)	96.0 (95.6-96.4)	64.9 (47.5-79.8	0.53 (0.52-0.54)
Algorithm F	99.9 (99.8-99.9)	5.1 (3.3-7.5)	95.7 (95.3-96.1)	64.9 (47.5-79.8)	0.52 (0.51-0.53)
Algorithm G	99.7 (99.6-99.8)	8.8 (4.3-15.5)	99.0 (98.8-99.2)	27.0 (13.8-44.1)	0.54 (0.52-0.57)
Validation Subset					
Algorithm A	99.9 (99.9-99.9)	6.1 (3.0-10.9)	98.5 (98.3-98.8)	43.5 (23.2-65.5)	0.53 (0.51-0.55)
Algorithm B	99.9 (99.8-99.9)	3.1 (1.6-5.4)	96.5 (96.1-96.8)	52.2 (30.6-73.2)	0.52 (0.51-0.52)
Algorithm C	99.9 (99.8-99.9)	2.8 (1.4-4.8)	96.0 (95.6-96.3)	52.2 (30.6-73.2)	0.51 (0.51-0.52)
Algorithm D	99.8 (99.7-99.9)	37.5 (15.2-64.6)	99.9 (99.8-100.0)	26.1 (10.2-48.4)	0.69 (0.56-0.81)
Algorithm E	99.9 (99.8-99.9)	3.1 (1.6-5.4)	96.5 (96.1-96.8)	52.2 (30.6-73.2)	0.52 (0.51-0.52)
Algorithm F	99.9 (99.8-99.9)	2.8 (1.4-4.8)	96.0 (95.6-96.3)	52.2 (30.6-73.2)	0.51 (0.51-0.52)
Algorithm G	99.9 (99.8-99.9)	6.3 (3.1-11.3)	98.6 (98.4-98.8)	43.5 (23.2-65.5)	0.53 (0.51-0.55)

AUROC, area under the receiver operating characteristic curve; NPV, negative predictive value PPV, positive predictive value.
Performance metrics of best performing algorithms on development and validation subset. The best performing algorithm (in this case, A) is defined first by the highest specificity.

metrics.

Under varying clinical settings or locations, where varied amounts of administrative information might be available, or in the setting of different research needs, one algorithm could have more functionality over another. Claims-based epidemiological research, such as comparative effectiveness investigations, primarily benefit from diagnostic and confirmatory tools (algorithms) with high specificity and PPV. This is in part due to the decreased probability of misclassification of disease when applied in this fashion. However, claims-based algorithms with high specificity are also viable screening tools when both sensitivity and specificity are validated (Fox et al., 2005; Ogburn and VanderWeele, 2012), potentially increasing the utility of our best performing algorithm twofold.

There is a host of studies that have developed algorithms utilizing administrative data to identify PSE (Pitkänen et al., 2016). On the one hand, the explosion of studies that utilize widely available administrative data is a boon for epidemiological research, as it enables greater accuracy in estimating true disease and efficient collection of large quantities of data. On the other hand, errors in measuring disease status can be an important source of bias in these studies. In conducting studies, therefore, it is important to assess the quality of measurements. Most existing epidemiological studies do not typically generalize, due to the utilization of different types of administrative data, varying definitions of true disease, and different populations/subpopulations. Furthermore, many do not use validated methods. Taken together, it is no surprise that the estimates of PSE rates and prevalence vary.

In our reconstructed sample of 20,943 elderly Medicare beneficiaries during a three-year time window (2012–2014), we observed a stroke prevalence of 8.9% (i.e., 1872 patients with at least one claim for stroke). This is consistent with the 2018 report published by the AHA, which estimates stroke prevalence of approximately 6.3% (ages 60–79)-14.35% (age 80 +) (Benjamin et al., 2018). Of these beneficiaries with a claim for stroke, we observed a PSE prevalence of 2.4% (n = 44), which is also consistent with the lower end heterogeneous estimates of PSE prevalence (following stroke), estimated as low as 2.5% (Bladin et al., 2000; Graham et al., 2013; Jungehulsing et al., 2013; Pitkänen et al., 2016).

Of all epidemiological surveillance studies that have analyzed PSE or post-stroke seizure epidemiology in the past ten years (Graham et al., 2013; Jungehulsing et al., 2013; Merkler et al., 2018; Stefanidou et al., 2017), only one developed an identification method specific to the elderly subpopulation (Merkler et al., 2018). This is surprising, given the well-documented differences by age in the manifestations and etiology of epilepsy, as well as the approach to treatment (Brodie et al., 2009; Leppik, 2007). Our large, clearly defined sample size and development strategy supports the value and validity of our findings.

One additional strength is our reference-standard for epilepsy and PSE diagnosis. The most current study on PSE/post-stroke seizures did not have a reference-standard diagnosis to validate claims against (Merkler et al., 2018). Our reference-standard definition, i.e. abstraction of diagnosis from EHRs by an expert neurologist that subspecializes in epilepsy, improves on existing methods. Using one neurologist for data abstraction from linked longitudinal data served a threefold purpose: 1) it decreased the possibility of abstraction of erroneous data (e.g., misclassification or misdiagnosis of epilepsy and etiology from diagnostic data) from a less skilled research team member; 2) it decreased the possibility of misclassification across multiple reviewers (i.e. poor interrater reliability); 3) more comprehensive diagnostic and treatment information (e.g., discharge information, EEG, imaging data, and prescription data) across all levels of care resides in linked longitudinal EHRs compared to specialized (e.g., epilepsy) data registries.

Furthermore, their definition for a post-stroke seizure was any ICD-9 code of 345.xx after an inpatient discharge that was coded with stroke (Merkler et al., 2018). This fails to take into account the inaccuracy of single ICD-9 codes for epilepsy, which are known to have low sensitivity and specificity. Due to the feasibility of collecting medication data for our study, we were situated to improve on this approach and validate the use of AEDs. This is of particular importance to outcome assessments, which would benefit from the ability to distinguish prior AED users (e.g., patients prescribed an AED in the hospital for primary prophylaxis and continue after discharge) who go on to develop PSE from non-AED users who then develop PSE. As a result, our PSE definitions, which included codes for epilepsy, stroke, and AEDs, achieved high performance after validation in a split-sample approach.

4.1. Limitations

As demonstrated in our study, vast amounts of administrative data can be efficiently gathered and analyzed. However, an inherent limitation is that claims data may not provide a full clinical or diagnostic picture. Epilepsy is both underdiagnosed and misdiagnosed in the elderly due to a wide array of structural and age-related diseases (e.g., dementia symptoms, transient ischemic events) that manifest similarly to dyscognitive seizures. Although the identification of patients who might have been misdiagnosed or misclassified was outside the scope of our study, which sought to identify patients with PSE among those with a definitive diagnosis, our sampling approach mitigated some worries about erroneous diagnosis. For example, we avoided misdiagnosis due

to “leakage of information” (loss of information due to movement of patients from one insurance company to another) through the selection of beneficiaries continuously enrolled in the Medicare ACO (or until death).

Additionally, our algorithms were developed and validated using a well-defined population of ACO beneficiaries (i.e. community-dwelling elderly Medicare beneficiaries in the New England area). Thus, the generalizability of these algorithms to other age subpopulations, which report varied incidence of PSE, or populations with divergent administrative data might be limited. In the same vein, our sampling approach, which included only patients enrolled in the ACO, might limit generalizability, as patients enrolled in the ACO might have a selected level of education, or more severe disease.

Third, because we retrospectively analyzed Medicare claims between 2012 and 2014 for PSE identification, we utilized ICD-9 coded claims. This is consistent with the most recent claims-based, retrospective epidemiological studies on epilepsy or PSE (Ip et al., 2018; Merkler et al., 2018), as the United States only recently implemented ICD-10 coding in 2015. Our algorithm should be useful for current research groups that often have retrospective Medicare claims to study. In addition, other groups could use these algorithms as a starting place to validate claim-based diagnosis of PSE in ICD-10 data, and could use a similar identification strategy to identify other epilepsy etiologies (e.g., epilepsy due to hemorrhagic insult or neurodegeneration) with high specificity.

Furthermore, inherent to all claims-based research is that claims data does not encapsulate clinical symptoms and true diagnosis with 100% precision. Algorithms that employ claims-based variables must remain aware of these limitations. For example, our algorithms utilized EEG, exclusionary AED, and inclusionary cerebrovascular variables. Although the EEG variable contributed to a higher specificity and sensitivity in our best performing algorithm, it is worth noting that our sample frequently received EEGs for indications other than epilepsy, and the EEG impressions documented in EHRs did not always have a clear prognostic value for epilepsy. Likewise, incorporating the spectrum of AEDs into a claims-based algorithm remains a challenge. Prescription patterns within this drug class fluctuate due to systemic factors such as varying co-payment policies, changes in drug patent status, the training of the prescriber, or even regional prescribing patterns. Thus, our best performing algorithms utilized an exclusionary epilepsy-specific AED variable that potentially missed other newer generation antiepileptic drugs such as Zonisamide or Lacosamide (neither, however, were prescribed in any PSE patients in our sample). Indeed, stroke claims do not always accurately capture specific stroke subtypes (e.g., an ischemic stroke with hemorrhagic transformation might be coded only as a hemorrhagic stroke). As a result, we created an inclusive cerebrovascular variable to ensure we did not miss any ischemic codes due to potential miscoding.

Finally, we are unable to accurately measure incident PSE using our algorithms. Due to our focus on confirming disease status among those who have a claims-based diagnosis for the disease, our algorithms stress specificity over sensitivity. In some scenarios this is not desirable. Although our algorithms are functional for tracking disease detection over time, the risk of capturing a high number of false negative PSE cases would hinder efforts aimed at tracking current disease burden. Unavailability of data concerning the first diagnosis of either stroke or epilepsy further exacerbates this issue. To generate algorithms to estimate PSE incidence, future efforts might develop more nuanced algorithms that incorporate not only diagnosis and treatment claims, but also include varying time-windows of claims to validate against a reference-standard diagnosis date in EHR data.

5. Conclusions

In this validation study, we developed and validated multiple Medicare claims-based algorithms to identify PSE as a specific etiological classification of epilepsy in the community-dwelling elderly population with high specificity and predictive validity. This rigorous identification strategy is the first step towards better population-based studies on epilepsy outcomes and care quality.

Disclosures

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Data statement

Lidia M.V.R. Moura had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The data that support the findings of this study are available from the corresponding author (LM) upon reasonable request

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Statistical analysis revised by the statistician Hang Lee, PhD, Massachusetts General Hospital through the Harvard Catalyst statistical consulting program.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.02.002.

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