



Stroke risk and outcomes in epilepsy patients: Two retrospective cohort studies based on National Health Insurance in Taiwan

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HIGHLIGHTS

- Patients with epilepsy were at significantly increased risk of stroke during the long-term follow-up period.
- Epilepsy history was associated with stroke risk in all ages and both sex.
- Post-stroke outcome was associated with epilepsy.

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ABSTRACT

Background and aims: The risk of stroke in epileptic patients and the impact of epilepsy history on stroke patients' outcome have not been studied completely. Our purpose is to evaluate whether patients with epilepsy have increased risk of stroke or post-stroke mortality.

Methods: In Study I, we conducted a retrospective cohort study of 6746 patients with newly diagnosed epilepsy and 26,984 persons without epilepsy between 2000 and 2008, in the database of National Health Insurance in Taiwan. The incidences and risks of stroke during the follow-up period were compared between cohorts until the end of 2013. In Study II, we conducted a nested cohort study of 484,990 hospitalized patients with newly diagnosed stroke between 2000 and 2009. We compared the short-term mortality and complications during stroke admission between stroke patients with previous epilepsy and those without epilepsy.

Results: The epileptic cohort had an increased stroke risk (hazard ratio [HR] 2.24, 95% CI 2.02 to 2.49). The relationship between epilepsy and stroke risk remains significant in every age group and both sexes. Among hospitalized stroke patients, history of epilepsy was associated with complications, including pneumonia (odds ratio [OR] 1.08, 95% CI 1.00 to 1.18), urinary tract infection (OR 1.16, 95% CI 1.08 to 1.26), and longer stay ($p < 0.0001$) during the index stroke admission.

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; OR, odds ratio

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Conclusions: Epileptic patients face increased stroke risk and adverse outcomes of stroke admission. It is necessary to develop a prevention strategy for stroke in epileptic patients.

1. Introduction

Stroke was identified as one of the most common causes of death and disability worldwide [1,2]. The estimation shows that 16 million people have a first stroke, 5.7 million die of stroke, and 5 million stroke patients face disabilities, annually [3]. A worldwide review showed a 42% decrease in stroke incidence in high-income countries, whereas the reported incidence in low-income and middle-income countries more than doubled. Between 2000 and 2008, the incidence of first-ever stroke in low- and middle-income countries exceeded that in high-income countries by 20% [4].

Epilepsy is a chronic neurological disorder with estimated prevalence rates of 0.2–4.1% in general populations worldwide [5]. Patients with epilepsy often develop comorbidities affecting physical, mental and behavioral functions, such as dementia and cardiac, gastrointestinal, respiratory, metabolic and psychiatric disorders [6,7].

While epilepsy has been considered a complication for stroke [8], whether epilepsy increases the risk of stroke is not well understood [9,10]. As epilepsy's impact on post-stroke status remains unknown, it is useful to identify and quantify stroke risk factors in patients with epilepsy. In this investigation, we used reimbursement claims of insurance data to assess stroke risk in epileptic patients in a retrospective cohort study. We also conducted a nested stroke cohort study to further research epilepsy's role in post-stroke mortality.

2. Materials and methods

2.1. Source of data

The Taiwan's National Health Insurance systems covered more than 99% of the nation's 23 million people by 2009. Claims data included patients' personal characteristics and records of all outpatient and inpatient medical services from 1996 to 2013. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used for diagnoses. Taiwan's National Health Research Institutes provide the National Health Insurance Research Database for public access. Patient information, including date of birth, sex, residence, and income (inferred from insurance fees), was retrieved. The National Health Insurance Bureau conducts regular sample cross-checks of each hospital claim with medical records and administers punitive measures for coding infractions, followed by tying a hospital reimbursement level to the patient severity profile. Thus, hospital interests are best served by accurate coding of diagnoses and care items, and the precision of major diagnostic codes, procedure codes, and underlying cause of death in the National Health Insurance Research Database is generally recognized. Our previous studies based on the National Health Insurance Research Database have been accepted by journals worldwide [11–14].

2.2. Ethical approval

Insurance reimbursement claims used in this study were from Taiwan's National Health Insurance Research Database, which is available for public access [11–14]. This study was conducted in accordance with the Helsinki Declaration. To protect personal privacy, the electronic database was decoded, with patient identifications scrambled for further public access for research. According to National Health Research Institutes regulations, informed consent is not required because of the use of decoded and scrambled patient identification. However, this study was evaluated and approved by Institutional

Review Boards of Taipei Medical University (TMU-JIRB-201705063; TMU-JIRB-201705065) and E-Da Hospital (EDA-JIRB-2017004; EDA-JIRB-2017005; EDA-JIRB-2017144).

2.3. Patient and public involvement

The development of the research question and outcome measures was not informed by patients' priorities, experience, and preferences. Patients were not involved in the design, recruitment, and conduct of this study. The results of this study will not be disseminated to study participants. Patient advisers are thanked in the Acknowledgements section.

2.4. Study design and population

In this longitudinal cohort of one million insured individuals (Study I), we examined the insurance medical records and identified the epilepsy cohort including 6746 patients aged 20 years or older, with new diagnosis of epilepsy between 2000 and 2008 (details are described in the flowchart of Fig. 1). These patients had no previous record of diagnosis or treatment for epilepsy from the database since 1996 and had no history of stroke before the index date. To more strictly identify patients with epilepsy, this study required at least one visit for outpatient or inpatient medical services with a principal diagnosis of epilepsy. During the same index period, we used frequency matching (by age and sex; case-control ratio = 1:4) to identify a non-epilepsy cohort including 26,984 people aged 20 years or older from the one-million population. This non-epilepsy cohort had no epilepsy diagnosis and no history of stroke before the index date. Patients with any diagnosis of stroke between 1 January, 1996 and 31 December, 2008 were excluded to ensure that all study participants were free of stroke at the start of both cohorts. Follow-up started 1 January, 2000 and lasted until censoring due to death, loss to follow-up, or other causes by 31 December, 2013. We sought to determine whether individuals with epilepsy faced an increased risk of stroke.

To investigate the impact of epilepsy on post-stroke outcomes (Study II), a nested stroke cohort study was conducted using data from the National Health Insurance Research Database. We identified 484,990 hospitalized patients with stroke between 2000 and 2009, including 6913 patients with pre-stroke epilepsy and 478,077 without epilepsy history. We compared post-stroke pneumonia, urinary tract infection, and mortality for a 30-day period after stroke between stroke patients with and without pre-stroke epilepsy.

2.5. Measures and definitions

We identified income status by defining low-income patients as those qualifying for waived medical copayment, because this status is verified by the Bureau of National Health Insurance. Population density was calculated by dividing the population (persons) by the area (square kilometers) for each administrative unit of Taiwan, and then sorting these areas into quartiles of low, moderate, high, and very high urbanization. These categories were used as surrogates for residential urbanization.

We used codes from the ICD-9-CM to define coexisting medical conditions and post-stroke complications. Pre-stroke epilepsy (ICD-9-CM 345) was defined as an exposure and this definition was used in our previous studies [11,12,15]. Subtypes of epilepsy were also recorded as generalized epilepsy (345.0, 345.1), petit mal status (345.2), grand mal status (345.3), partial epilepsy (345.4, 345.5), epilepsia partialis

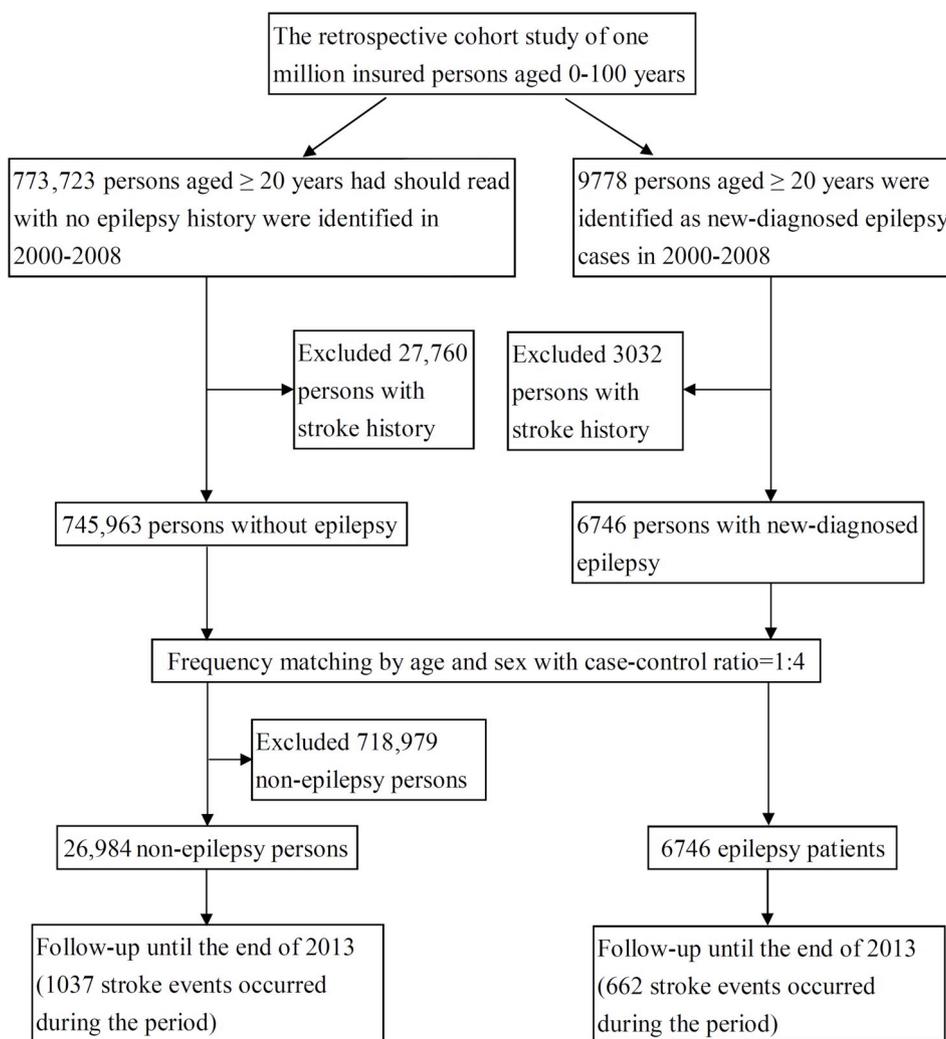


Fig. 1. The process of selection of study subjects for Study I.

continua (345.7), and other unspecified epilepsy (345.8, 345.9). Stroke cases were identified by ICD-9-CM 430–437 in the National Health Insurance Research Database and the validation was also completed in previous reports [13,14,16–20]. Coexisting medical conditions were determined from medical claims from the follow-up period and included mental disorders (ICD-9-CM 290–319), hypertension (ICD-9-CM 401–405), chronic obstructive pulmonary disease (ICD-9-CM 490–496), traumatic brain injury (ICD-9-CM 800–804, 850–854), coronary artery disease (ICD-9-CM 410–414), diabetes (ICD-9-CM 250), migraine (ICD-9-CM 346), alcohol-related illness, hyperlipidemia (ICD-9-CM 272.0, 272.1, and 272.2), liver cirrhosis (ICD-9-CM 571), heart failure (ICD-9-CM 428), smoking cessation (administration code IC07) and renal dialysis (administration code D8, D9). We defined alcohol-related illnesses, including alcoholic psychoses (ICD-9-CM code 291), alcohol dependence syndrome (ICD-9-CM code 303), alcohol abuse (ICD-9-CM code 305), alcoholic fatty liver (ICD-9-CM code 571.0), acute alcoholic hepatitis (ICD-9-CM code 571.1), alcoholic cirrhosis of the liver (ICD-9-CM code 571.2), and alcoholic liver damage (ICD-9-CM code 571.3). Complications after stroke were analyzed as secondary outcomes, including pneumonia (ICD-9-CM 480–486), and urinary tract infection (ICD-9-CM 599.0). In the nested stroke cohort study, we also applied the stroke severity index (SSI) as one covariate validated in previous studies [18–20]. Post-stroke 30-day, 90-day, and 120-day in-hospital mortality was also considered an outcome in the nested stroke cohort study.

2.6. Statistical analysis

Our study used Chi-square tests to compare sociodemographic characteristics and coexisting medical conditions between people with and without epilepsy. We calculated the hazard ratios (HRs) with 95% CIs for risk of stroke after epilepsy, adjusting for age, sex, low income, urbanization, mental disorders, hypertension, chronic obstructive pulmonary disease, traumatic brain injury, coronary artery disease, diabetes, migraine, alcohol-related illness, hyperlipidemia, liver cirrhosis, heart failure, smoking cessation, and renal dialysis in multivariate Cox proportional hazards regression models. The sex- and age-stratified analyses for the adjusted HRs of stroke associated with epilepsy were calculated. In the nested stroke cohort study, the sociodemographics and coexisting medical conditions between hospitalized stroke patients with and without previous epilepsy were compared by using Chi-square tests.

The adjusted odds ratios (ORs) and 95% CIs of post-stroke pneumonia, urinary tract infection, and mortality associated with pre-stroke epilepsy were calculated in the multivariate logistic regressions with adjustment for age, sex, low income, urbanization, mental disorders, hypertension, chronic obstructive pulmonary disease, traumatic brain injury, coronary artery disease, diabetes, migraine, alcohol-related illness, hyperlipidemia, liver cirrhosis, heart failure, smoking cessation, and renal dialysis. SAS Version 9.1 (SAS Institute Inc., Cary, NC, USA) statistical software was used for data analyses; two-sided $p < 0.05$ indicated significant differences between groups.

3. Results

After the frequency matching with age and sex, patients with epilepsy had higher proportions of low-income status ($p < 0.0001$), co-existing medical conditions ($p < 0.0001$), and cardiovascular medications ($p < 0.0001$) than the cohort without epilepsy (Table 1).

Table 2 showed that higher incidence of stroke was found in patients with epilepsy than those without epilepsy (10.4 vs. 4.27 per 1000 person-years) during the follow-up period. The corresponding HR of stroke associated with epilepsy was 2.24 (95% CI 2.02 to 2.49). The association between epilepsy and stroke risk was more significant in males (HR 2.47, 95% CI 2.16 to 2.83) than in females (HR 1.93, 95% CI 1.63 to 2.29). Patients with epilepsy were at greater risk of stroke in all age groups, particularly those 20–39 years of age (HR 4.33, 95% CI 2.94 to 6.37).

Compared with people without epilepsy, the epileptic cohort with alcohol-related illness (OR 3.97, 95% CI 3.17 to 4.97), low income (OR 3.62, 95% CI 2.90 to 4.53), traumatic brain injury (OR 3.46, 95% CI 2.96 to 4.05), epilepsy partialis continua (OR 3.27, 95% CI 2.11 to 5.07), grand mal status (OR 3.10, 95% CI 2.14 to 4.47), general seizure (OR 3.03, 95% CI 2.32 to 3.96), emergency care for epilepsy (OR 2.97, 95% CI 2.48 to 3.57), intractable epilepsy (OR 2.80, 95% CI 2.27 to 3.47), inpatient care for epilepsy (OR 2.78, 95% CI 2.20 to 3.50), and petit mal status (OR 2.61, 95% CI 1.24 to 5.50) had a significantly higher risk of stroke during the follow-up period (Table 3).

Among 484,990 hospitalized stroke patients (Table 4), higher proportions of patients with epilepsy than patients without epilepsy were noted among males ($p < 0.0001$), younger people ($p < 0.0001$), low income ($p < 0.0001$), hypertension ($p < 0.0001$), mental disorders ($p < 0.0001$), chronic obstructive pulmonary disease ($p < 0.0001$), diabetes ($p < 0.0001$), traumatic brain injury ($p < 0.0001$), coronary artery disease ($p = 0.0187$), alcohol-related illness ($p < 0.0001$), atrial

fibrillation ($p < 0.0001$), liver cirrhosis ($p < 0.0001$), heart failure ($p = 0.0263$), hyperlipidemia ($p < 0.0001$), renal dialysis ($p < 0.0001$), and migraine ($p = 0.0002$). There were higher proportions of general ward stay ($p < 0.0001$), nasogastric intubation ($p < 0.0001$), urinary catheterization ($p < 0.0001$), intensive care unit stay, suctioning ($p < 0.0001$), and bacterial sensitivity test ($p < 0.0001$) were found in stroke patients with epilepsy history than those without epilepsy (not showed in the tables).

In Table 5, patients with epilepsy had higher risk of pneumonia (OR 1.08, 95% CI 1.00 to 1.18), and urinary tract infection (OR 1.16, 95% CI 1.08 to 1.26) after stroke compared with those without epilepsy. During the index stroke admission, the length of hospital stay was higher in epileptic patients than in people without epilepsy ($p < 0.0001$).

4. Discussion

Our reports showed that patients with epilepsy in all age groups were at significantly increased risk of stroke in a socioeconomics-associated, disease-specific pattern in the retrospective cohort study. In particular, hospitalized stroke patients with previous epilepsy had increased pneumonia, urinary tract infection, and length of stay after admission in the nested cohort study. Our current investigation may be the first study to investigate the epileptic patient's characteristics and severity associated with stroke risk, and the first study to validate the relationship of previous epilepsy and post-stroke adverse outcomes.

Age, sex, low income, hypertension, coronary artery disease, heart failure, diabetes, traumatic brain injury, smoking, liver cirrhosis, alcohol-related illness, hyperlipidemia, renal dialysis and mental disorders were associated with stroke [21,22]. Unlike previous studies that may be limited by several confounding factors [9,10], the present study used multivariate regression models to reduce confounding stroke-

Table 1

Sociodemographics, coexisting medical conditions, and stroke in people with and without epilepsy.

	No epilepsy (N = 26,984)		Epilepsy (N = 6746)		p value
	n	(%)	n	(%)	
Sex					1.0000
Female	11,800	(43.7)	2950	(43.7)	
Male	15,184	(56.3)	3796	(56.3)	
Age, years					1.0000
20-29	5464	(20.3)	1366	(20.3)	
30-39	5208	(19.3)	1302	(19.3)	
40-49	5512	(20.4)	1378	(20.4)	
50-59	3700	(13.7)	925	(13.7)	
60-69	2892	(10.7)	723	(10.7)	
≥70	4208	(15.6)	1052	(15.6)	
Low income	821	(3.0)	695	(10.3)	< 0.0001
Coexisting medical conditions					
Mental disorders	8083	(30.0)	4120	(61.1)	< 0.0001
Hypertension	7077	(26.2)	2241	(33.2)	< 0.0001
COPD	5339	(19.8)	1981	(29.4)	< 0.0001
Traumatic brain injury	2140	(7.9)	1619	(24.0)	< 0.0001
Coronary artery disease	2755	(10.2)	1096	(16.3)	< 0.0001
Diabetes	3359	(12.5)	1194	(17.7)	< 0.0001
Migraine	1668	(6.2)	825	(12.2)	< 0.0001
Alcohol-related illness	915	(3.4)	860	(12.8)	< 0.0001
Hyperlipidemia	2731	(10.1)	837	(12.4)	< 0.0001
Liver cirrhosis	1428	(5.3)	660	(9.8)	< 0.0001
Heart failure	837	(3.1)	349	(5.2)	< 0.0001
Smoking cessation	783	(2.9)	273	(4.1)	< 0.0001
Renal dialysis	221	(0.8)	161	(2.4)	< 0.0001
Atrial fibrillation	235	(0.9)	75	(1.1)	0.0637
Type of medication					
Lipid-lowering agents	6053	(22.4)	1934	(28.7)	< 0.0001
Anticoagulant	1133	(4.2)	598	(8.9)	< 0.0001
Anti-platelet agents	893	(3.3)	396	(5.9)	< 0.0001

COPD, chronic obstructive pulmonary disease.

Table 2
Incidence and risk of stroke for cohorts with and without epilepsy.^a

	n	Person-years	Stroke events	Incidence ^b	HR	(95% CI) ^c
Epilepsy						
No	26,984	243,018	1037	4.27	1.00	(reference)
Yes	6746	63,568	662	10.4	2.24	(2.02–2.49)
Female						
No epilepsy	11,800	106,910	414	3.87	1.00	(reference)
Epilepsy	2950	28,442	226	7.95	1.93	(1.63–2.29)
Male						
No epilepsy	15,184	136,108	623	4.58	1.00	(reference)
Epilepsy	3796	35,126	436	12.4	2.47	(2.16–2.83)
Age 20–39 years						
No epilepsy	10,672	101,565	54	0.53	1.00	(reference)
Epilepsy	2668	27,935	94	3.36	4.33	(2.94–6.37)
Age 40–49 years						
No epilepsy	5512	51,032	106	2.08	1.00	(reference)
Epilepsy	1378	13,482	118	8.75	2.95	(2.17–4.01)
Age 50–59 years						
No epilepsy	3700	32,377	156	4.82	1.00	(reference)
Epilepsy	925	8114	130	16.0	3.10	(2.40–4.01)
Age 60–69 years						
No epilepsy	2892	25,380	245	9.65	1.00	(reference)
Epilepsy	723	6349	121	19.1	1.78	(1.42–2.24)
Age ≥ 70 years						
No epilepsy	4208	32,663	476	14.6	1.00	(reference)
Epilepsy	1052	7689	199	25.9	1.64	(1.38–1.95)
0 medical condition						
No epilepsy	10,162	93,071	107	1.15	1.00	(reference)
Epilepsy	836	8309	52	6.26	5.79	(4.08–8.22)
1 medical condition						
No epilepsy	6663	59,776	239	4.00	1.00	(reference)
Epilepsy	1500	14,772	112	7.58	2.64	(2.10–3.32)
2 medical conditions						
No epilepsy	4537	40,517	254	6.27	1.00	(reference)
Epilepsy	1531	14,620	141	9.64	2.06	(1.67–2.55)
≥ 3 medical conditions						
No epilepsy	5622	49,653	437	8.80	1.00	(reference)
Epilepsy	2879	25,867	357	13.8	1.79	(1.55–2.06)

The hazard ratios of hemorrhagic stroke and ischemic stroke associated with epilepsy were 2.27 (95% CI 1.80–2.85) and 1.91 (95% CI 1.62–2.26), respectively; age ($p < 0.0001$), sex ($p < 0.0001$), and number of medical conditions ($p < 0.0001$) were all effects modifiers in the association between epilepsy and stroke incidence. The interaction terms epilepsy*sex ($p < 0.0001$), epilepsy*age ($p < 0.0001$), and epilepsy*medical conditions ($p < 0.0001$) were significantly associated with stroke risk.

CI = confidence interval; HR = hazard ratio.

^a There were 552 subjects (51 in epilepsy group) lost to follow-up (quit insurance coverage due to emigration abroad or missing population) and 1067 people died (469 in epilepsy group) during the follow-up period.

^b Per 1000 person-years.

^c Adjusted for all covariates listed in Table 1.

Table 3
Association between characteristics of epileptic patients and risk of stroke.

Characteristics of epileptic patients	Risk of stroke				
	n	Events	Incidence	HR	(95% CI) ^a
No epilepsy	26,984	1037	4.27	1.00	(reference)
Epileptic patients with					
Alcohol-related illness	860	102	13.4	3.97	(3.17–4.97)
Low income	695	90	13.8	3.62	(2.90–4.53)
Traumatic brain injury	1619	207	13.6	3.46	(2.96–4.05)
Epilepsia partialis continua	172	21	13.2	3.27	(2.11–5.07)
Grand mal status	234	30	13.5	3.10	(2.14–4.47)
General seizure	544	62	11.1	3.03	(2.32–3.96)
Emergency care for epilepsy	1466	151	10.8	2.97	(2.48–3.57)
Intractable epilepsy	998	100	9.96	2.80	(2.27–3.47)
Inpatient care for epilepsy	756	84	11.0	2.78	(2.20–3.50)
Petit mal status	76	7	9.60	2.61	(1.24–5.50)
Other unspecified epilepsy	4867	459	9.77	2.19	(1.95–2.47)
Severe mental disorders	1341	111	8.70	2.18	(1.75–2.71)
Partial epilepsy	951	74	7.80	2.15	(1.69–2.73)

CI = confidence interval; HR = hazard ratio.

^a Adjusted for all covariates listed in Table 1.

Table 4
Characteristics of hospitalized stroke patients with and without epilepsy.

	No epilepsy (N = 478,077)		Epilepsy (N = 6913)		p value
	n	(%)	n	(%)	
Sex					< 0.0001
Female	199,158	(41.7)	2363	(34.2)	
Male	278,919	(58.3)	4550	(65.8)	
Age, years					< 0.0001
20-29	3188	(0.7)	173	(2.5)	
30-39	10,706	(2.2)	382	(5.5)	
40-49	39,278	(8.2)	890	(12.9)	
50-59	78,355	(16.4)	1223	(17.7)	
60-69	114,964	(24.1)	1436	(20.8)	
70-79	148,114	(31.0)	1869	(27.0)	
≥80	83,472	(17.5)	940	(13.6)	
Low income	28,723	(6.0)	884	(12.8)	< 0.0001
Coexisting medical conditions					
Hypertension	226,021	(47.3)	2853	(41.3)	< 0.0001
Mental disorders	79,619	(16.7)	2206	(31.9)	< 0.0001
COPD	70,877	(14.8)	1516	(21.9)	< 0.0001
Diabetes	112,814	(23.6)	1478	(21.4)	< 0.0001
Traumatic brain injury	18,944	(4.0)	958	(13.9)	< 0.0001
Coronary artery disease	61,216	(12.8)	951	(13.8)	0.0187
Alcohol-related illness	7585	(1.6)	558	(8.1)	< 0.0001
Atrial fibrillation	22,099	(4.6)	424	(6.1)	< 0.0001
Liver cirrhosis	11,697	(2.5)	343	(5.0)	< 0.0001
Heart failure	19,708	(4.1)	322	(4.7)	0.0263
Renal dialysis	9093	(1.9)	255	(3.7)	< 0.0001
Hyperlipidemia	20,199	(4.2)	214	(3.1)	< 0.0001
Migraine	7020	(1.5)	164	(2.4)	< 0.0001
Smoking cessation	2757	(0.6)	44	(0.6)	0.5148
Type of stroke					< 0.0001
Ischemic stroke	300,696	(62.9)	3902	(56.4)	
Hemorrhagic stroke	116,545	(24.4)	1933	(28.0)	
Other stroke	60,836	(12.7)	1078	(15.6)	
Type of medication					
Lipid-lowering agents	116,188	(24.3)	1428	(20.7)	< 0.0001
Anticoagulant	64,004	(13.4)	1001	(14.5)	0.0081
Anti-platelet agents	40,205	(8.4)	569	(8.2)	0.5947
Stroke severity index					
General ward stay	325,952	(68.2)	4964	(71.8)	< 0.0001
Nasogastric intubation	109,449	(22.9)	2187	(31.6)	< 0.0001
Urinary catheterization	101,014	(21.1)	1798	(26.0)	< 0.0001
Intensive care unit stay	99,103	(20.7)	1625	(23.5)	< 0.0001
Suctioning	58,911	(12.3)	1276	(18.5)	< 0.0001
Bacterial sensitivity test	64,586	(13.5)	1266	(18.3)	< 0.0001
Osmotherapy	78,442	(16.4)	1062	(15.4)	0.0197

COPD, chronic obstructive pulmonary disease.

related factors when investigating associations between epilepsy and stroke.

In the age-stratified analysis, our study showed stroke risk increased with age. However, the relationship between epilepsy and stroke risk was more significant in the younger age group. Several possible reasons might explain this striking finding: first, etiologies and clinical manifestations for early-onset and late-onset epilepsy are quite different. The

most common causes of epilepsy in children and young adults are idiopathic disorders, inflammation, congenital vascular anomalies and mesial temporal sclerosis. Cerebrovascular disease, neurodegenerative disease, tumors, and traumatic brain injury were considered as common causes of epilepsy in the elderly [23,24]. Seizures resulting from idiopathic or inflammatory processes are usually of diffuse pattern, with generalized tonic-clonic seizure being the most common clinical

Table 5
Outcomes after stroke for patients with and without previous epilepsy.^a

Post-stroke outcomes	No epilepsy (N = 478,077)				Epilepsy (N = 6913)			
	Events	(%)	OR	(95% CI)	Events	(%)	OR	(95% CI)
Mortality	14,290	2.99	1.00	(reference)	237	3.43	1.01	(0.88–1.16)
Pneumonia	41,919	8.77	1.00	(reference)	743	10.75	1.08	(1.00–1.18)
UTI	53,917	11.28	1.00	(reference)	877	12.69	1.16	(1.08–1.26)
Length of stay, days ^b			8 (4–15)				8 (5–17)	

CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

^a Adjusted for all covariates listed in Table 4. The ORs of 90-day mortality and 120-day mortality associated with epilepsy history were 1.07 (95% CI 0.95–1.20) and 1.10 (95% CI 0.99–1.23), respectively.

^b Median (Q1–Q3); $p < 0.0001$ calculated by Wilcoxon rank-sum test.

presentation [25]. However, seizures originating from cerebrovascular disease, trauma or tumor are usually evoked by focal epileptic discharges around the lesion sites and most frequently recognized by complex or simple partial seizure [23,26,27]. Unlike generalized tonic-clonic seizures in young people (65%), it is relatively rare in older patients (26%).

Second, generalized tonic-clonic seizures are also rare in the elderly. As epileptogenesis involves some hypoxia-induced process of programmable cell death [28,29], different seizure patterns imply variations in the extent of brain hypoxia and stroke risk. Because diffuse types of epileptogenic spikes compromise global or regional cerebral perfusion more than focal spikes, chronic or other cerebral blood flow deprivation would increase stroke risk.

Third, medical control of late-onset epilepsy with anti-epileptic medications is relatively simple, since the clinical presentation tends to be focal rather than generalized seizures that can be controlled in most patients with low doses of a single anti-epileptic drug. Drug-resistant epilepsy is uncommon in the elderly patients, whereas early-onset epilepsy carries a worse prognosis due to the higher possibility of medical intractability. Multiple anti-epileptic drugs may be needed to control complex and generalized seizures responsible for most early-onset epilepsy [28,30]. Patients exposed to anti-epileptic drugs may be more likely to experience more risk of vascular diseases such as stroke. Previous investigations also reported that cytochrome P450 enzyme-inducing anti-epileptic drugs such as carbamazepine increase serum levels of lipid profiles [31,32]. Previous studies showed the exposure of heavy dosage and prolonged duration of anti-epileptic drug may predict acceleration of atherosclerosis and it represented a biological gradient relationship to increased stroke risk independent on other potential confounders such as age, gender, and oxidative stress [33,34].

Fourth, age is closely related to cerebrovascular disease and other medical diseases such as hypertension, diabetes, coronary artery disease, hypercholesterolemia, or renal disease [35]. Although incidence and risk of stroke increased as age increased, as shown in our study, the hazard ratio was lower in older age groups because of the diluting effect of these comorbidities that increase with age. Our finding of higher hazard ratio of stroke in younger age groups was similar to previous findings [36]; however, the authors did not offer additional explanations for this phenomenon.

Our main findings showed that epileptic patients face increased risk of subsequent stroke. From the findings of previous studies [28,29,33,34,37,38], we hypothesized that the processes of chronic hypoxia and programmed cell death induced by recurrent seizures as well as atherosclerosis associated with anti-epileptic drug exposure all contribute to cerebrovascular events. Our current results also showed that stroke patients with previous epilepsy history have higher post-stroke complications, notably urinary tract infection and pneumonia. Epilepsy is known to have higher mortality than the general population. In the United Kingdom, pneumonia, cancer, and stroke are identified as the commonest causes of death of patients with newly diagnosed epilepsy [39]. Another study ranked urinary tract infection as the most common of ten comorbidities in patients, especially women, with epilepsy [40]. However, we had not found the association between epilepsy history and stroke mortality in this study. Stroke *per se* is a critical disease that needs intensive care frequently. It is not surprising the impact of epilepsy history on short-term mortality after stroke because the severity of stroke during the index admission may dilute the influence of epilepsy history.

Our study shows that stroke patients with previous history of epilepsy are prone to higher complications of pneumonia and urinary tract infection, which are inherited comorbidities of epilepsy. While there is no convincing evidence of an association between epilepsy and infection or compromised immune system, diabetes is one of the most common comorbidities of epilepsy, which may contribute to the higher rate of infection.

This study has limitations: first, we identified epilepsy based on

physician diagnoses in the insurance claims data. It is difficult to differentiate a single episode of seizure from recurrent seizures (epilepsy). Inclusion of patients with only a single seizure may underestimate the risk of associated subsequent stroke and complications in stroke patients with previous epilepsy. Second, the information on socio-economics, lifestyle factors (smoking and alcohol consumption), biochemical measures (blood pressure and glucose), and clinical scores (the National Institutes of Health Stroke Scale) was unavailable in the insurance database. These factors may contribute to confounding effects when analyzing associations between epilepsy and risk of stroke. Third, exploring the Taiwanese population should be cautioned because the traditional Chinese medicine is also covered in the National Health Insurance and its one-year prevalence of utilization reached more than 30% [41]. The therapeutic effect of traditional Chinese medicine is complex and the interaction between traditional Chinese medicine and conventional biomedical medicine could not be evaluated in this study.

In addition, most seizure or epilepsy was diagnosed by semiology. Some presentations nonspecific to epilepsy, such as confusion or amnesia, could be misdiagnosed as dementia or other neurodegenerative diseases. Finally, we lacked detailed information about the severity, duration, and frequency of epilepsy history. Recent newly diagnosed epilepsy may have different impact than long-term history of epilepsy. Prescriptions for anti-epileptic drugs (single or multiple, type of drugs) are also not available for subgroup analysis.

In conclusion, we reported the relationship between epilepsy and incident risk of stroke in the long-term follow-up study based on insurance data. In addition to finding that previous history of epilepsy increased complications of stroke, this study further documented that hazard ratio of stroke is higher in younger age groups. It is necessary to develop prevention strategy for stroke in epileptic patients, particularly in younger age groups.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

Sanford P.C. Hsu, Chun-Chieh Yeh, Yi-Chun Chou, Chun-Chuan Shih, Chaur-Jong Hu, Yih-Giun Cherng, Ta-Liang Chen, and Chien-Chang Liao participated in conceptualization, data curation, investigation, methodology, project administration, resources, writing - review & editing. Sanford P.C. Hsu, Yih-Giun Cherng, Ta-Liang Chen, and Chien-Chang Liao participated in funding acquisition, supervision, validation, visualization, and writing - original draft. Chien-Chang Liao contributed to formal analysis, and software.

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