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ORIGINAL RESEARCH

Epilepsy is associated with higher subsequent mortality risk in patients after stroke: a population-based cohort study in Taiwan

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Tomor Harnod[1,2]
Cheng-Li Lin[3,4]
Chia-Hung Kao[5–7]

[1]Department of Neurosurgery, Hualien Tzu Chi General Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan; [2]College of Medicine, Tzu Chi University, Hualien, Taiwan; [3]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan; [4]College of Medicine, China Medical University, Taichung, Taiwan; [5]Graduate Institute of Biomedical Sciences, College of Medicine, China Medical University, Taichung, Taiwan; [6]Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan; [7]Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan

Objective: To use the National Health Insurance Research Database (NHIRD) of Taiwan to determine whether patients with poststroke epilepsy (PSE) in Taiwan have an increased risk of mortality.

Methods: We analyzed the data from the NHIRD of patients (≥40 years) who had received stroke diagnoses between 2000 and 2012. The patients with stroke were divided into PSE and poststroke non-epilepsy (PSN) cohorts and compared against a sex-, age-, comorbidity-, and index-date-matched cohort from normal population. We calculated adjusted HRs (aHRs) and 95% CIs of all-cause mortality risk in these cohorts after adjustment for age, sex, and comorbidities.

Results: Among the poststroke patients, 12.14% constituted the PSE cohort. The cumulative mortality rate was considerably higher in the PSE than in the PSN cohort. The PSE (aHR=4.18, 95% CI=3.91–4.48) and PSN (aHR=1.90, 95% CI=1.83–1.98) cohorts were associated with higher risks of mortality than the comparison cohort. Furthermore, advanced age (≥65 years), male sex, alcohol-related illness, chronic obstructive pulmonary disease, coronary artery disease, diabetes, hypertension, asthma, and cancer would further increase the risk of mortality after a stroke event.

Conclusion: The mortality risk in poststroke patients is approximately two times the likelihood in those with PSE than in those without, and approximately four times higher than that in the normal population. Our findings provide crucial information for clinicians and the government to improve survival after stroke.

Keywords: cohort study, epilepsy, mortality, stroke, National Health Insurance

Introduction

Worldwide, stroke is a major neurovascular disease that usually occurs suddenly. Patients who survive the acute stage of a stroke usually have various disabilities and comorbidities in their daily lives, thereby resulting in a long-term reduction in the quality of life. To our knowledge, stroke is the most common cause of disability and dependence in the adult population.[1–3]

Epilepsy is also a common neurological disease worldwide; it presents with repetitive seizure episodes and can damage the patient's brain. Epilepsy has a clinical prevalence of 0.5–1% in the general population.[4,5] Based on its etiology, poststroke epilepsy (PSE) is currently categorized as a structural epilepsy determined by the brain insult from a stroke.[6,7] Stroke is known to be one of the leading etiologies of adult epilepsy.[4,8] Patients who survive a stroke event may experience

Correspondence: Chia-Hung Kao
Graduate Institute of Biomedical Sciences, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan
Email d10040@mail.cmuh.org.tw; dr.kaochiahung@gmail.com

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PSE, and the incidence of PSE is approximately 3.1–11.5% in poststroke patients in developed Western countries.[9–11] Additionally, researchers reported that patients with epilepsy might have approximately two times higher mortality risk and a shorter life expectancy than those of the general population.[12] However, the extent of increase in the risk of mortality in patients with stroke and PSE in Taiwan remains unknown, and correlated risk factors could help prevent premature death in these patients. Therefore, additional investigation is required to understand the correlation between mortality risks in poststroke patients with or without PSE to elucidate future treatment strategies for the management of patients after stroke.

We used a nationwide, population-based database to investigate and compare the mortality risks and risk factors between Taiwanese patients with PSE and those patients with stroke without epilepsy (poststroke non-epilepsy, PSN) to elucidate future strategies for poststroke care and reduce the burden of poststroke care. The findings of this study might also aid the future development and implementation of effective treatment strategies in other developing Asian countries.

Methods

Data source

We conducted a population-based retrospective cohort study using the Longitudinal Health Insurance Database (LHID) of the National Health Insurance Research Database (NHIRD) of the Taiwan National Health Insurance (NHI) program. The NHI program began in March 1995 and has enrolled more than 99% of the 23 million residents of Taiwan.[13] Details regarding the LHID and NHI have been provided in previous studies.[14,15] This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115-CR3).

Study population

Patients aged ≥40 years who had received diagnoses of stroke (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 430–438) between January 1, 2000 and December 31, 2012 were included in the total stroke cohort. Although the International League Against Epilepsy (ILAE) recommendations for epilepsy classification have varied over time, we enrolled PSE and PSN patients by their ICD codes recorded in the NHIRD during the follow-up period that was from on the index date and continued until death, withdrawal from the database, or December 31, 2013. The patients in the total stroke cohort were further divided into two cohorts based on their poststroke epilepsy status: the PSE group included patients who had newly onset epilepsy (ICD-9-CM codes 345) after the stroke event, whereas the PSN group included patients who did not receive an epilepsy diagnosis during the follow-up period. Patients aged <40 years or who received epilepsy diagnoses before the stroke event were excluded. The data of patients with missing information of age or sex were excluded. The date of the first PSE diagnosis was defined as the index date, and the index date for the PSN group was a random month and day but with the identical index year to that of the matched patients in the PSE group. For each patient with stroke, two subjects from normal population without a history of stroke or epilepsy were randomly selected from the LHID as comparison cohort; the exclusion criteria used for selecting the total stroke cohort were used for selecting the comparison cohort. The comparison cohort was matched with the stroke cohort using a propensity score; this propensity score was calculated using logistic regression to estimate the probability of the assignment of a stroke status, given the baseline variables: age, sex, comorbidities of alcohol-related illness (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0, 571.1, 571.3, 790.3, and V11.3), anxiety disorders (ICD-9-CM 300), mental disorders (ICD-9-CM 290-319), insomnia (ICD-9-CM codes 307.4 and 780.5), depression (ICD-9-CM codes 296.2, 296.3, 296.82, 300.4, and 311), head injury (ICD-9-CM 850-854 and 959.01), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, and 496), coronary artery disease (CAD) (ICD-9-CM code 410-414), diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401-405), hyperlipidemia (ICD-9-CM 272), cancer (including brain tumor) (ICD-9-CM codes 140-208), asthma (ICD-9-CM code 493), and year of index date.

Statistical analysis

The baseline distribution of demographic characteristics and comorbidities was compared among the stroke cohorts (PSE and PSN) and the comparison cohort. Categorical variables were analyzed using the chi-square test, and the continuous variables of the baseline characteristics of the stroke and comparison cohorts were analyzed using the two sample independent t test. The Kaplan-Meier method was

used to estimate the cumulative incidence of death among the three cohorts (PSE, PSN, and comparison cohorts), and significance was determined using the log-rank test.

The incidence densities of death were calculated for different risk factors and stratified by age, sex, and comorbidity among the total stroke, PSE, PSN, and comparison cohorts. Univariable and multivariable Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs of mortality associated with the PSE and PSN cohorts and compared with those of the comparison cohort. Variables found to be statistically significant in the univariable model were further included in the multivariable model (including age, sex, comorbidies of alcohol-related illness, anxiety disorders, depression, head injury, COPD, coronary artery disease, diabetes, hypertension, hyperlipidemia, asthma, and cancer). All statistical analyses were performed using SAS statistical software (version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). A two-tailed *p*-value of <0.05 was considered statistically significant.

Data availability statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). Any researcher interested in accessing this dataset can submit an application form to the MOWH requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan MOHW address: No. 488, Sec. 6, Zhongxiao E. Road, Nangang District, Taipei City 115, Taiwan. Phone: +886 2 8590 6848.

Results

In total, we included 13,603 patients with stroke (87.86% and 12.14% constituted the PSN and PSE cohorts, respectively). The comparison cohort consisted of 27,207 subjects from normal population. The baseline characteristics of the three cohorts are presented in Table 1. The PSN and PSE cohorts had a higher (69.7 years) and lower (69.0 years) mean age, respectively, than the comparison cohort (mean age 69.3 years). Among the three cohorts, the majority of

Table 1 Distribution of age, sex, and comorbidities between stroke and comparison cohorts

	Total stroke N=13,603		Poststroke non-epilepsy N=11,952		Poststroke epilepsy N=1,651		Comparison cohort N=27,207		
	n	%	n	%	n	%	n	%	*P*-value^
Age, years									0.05
40–64	4,475	32.9	3,893	32.6	582	35.3	9,278	34.1	
65–74	4,064	29.9	3,612	30.2	452	27.4	8,033	29.5	
≥75	5,064	37.2	4,447	37.2	617	37.4	9,896	36.4	
Mean (SD)[§]	69.7	11.8	69.8	11.7	69.0	12.6	69.3	11.5	<0.001
Sex									0.86
Female	12,052	44.3	5,353	44.8	685	41.5	6,038	44.4	
Male	15,155	55.7	6,599	55.2	966	58.5	7,565	55.6	
Comorbidity									
Alcohol-related illness	633	4.65	548	4.59	85	5.15	1,351	4.97	0.17
Anxiety disorders	4,146	30.5	3,695	30.9	451	27.3	8,250	30.3	0.75
Mental disorders	7,663	56.3	6,708	56.1	955	57.8	15,152	55.7	0.22
Insomnia	9,741	71.6	8,448	70.7	1,293	78.3	19,456	71.5	0.84
Depression	1,373	10.1	1,186	9.92	187	11.4	2,797	10.3	0.56
Head injury	483	3.55	376	3.15	107	6.48	1,228	4.51	0.001
COPD	4,081	30.0	3,448	28.9	633	38.3	7,998	29.4	0.21
Coronary artery disease	6,441	47.4	5,719	47.9	722	43.7	12,632	46.4	0.08
Diabetes	3,545	26.1	3,127	26.2	418	25.3	6,875	25.3	0.08
Hypertension	11,953	87.9	10,483	87.7	1470	89.0	23,845	87.6	0.51
Hyperlipidemia	6,024	44.3	5,413	45.3	611	37.0	11,902	43.8	0.30
Asthma	1,994	14.7	1,712	14.3	282	17.1	4,098	15.1	0.28
Cancer (including brain tumor)	775	5.70	682	5.71	93	5.63	1,589	5.84	0.56

Notes: Chi-square test; [§]*t*-test; ^total stroke vs comparison cohort.

patients were male (55.2% in the PSN cohort, 58.5% in the PSE cohort, and 55.6% in the comparison cohort) (Table 1).

The median and range of follow-up in PSN cohort, PSE cohort, and comparison cohort were 4.21 (range=0.003–14.0), 3.05 (range=0.003–14.0), and 5.22 (range=0.003–14.0), respectively. As shown in Figure 1, the cumulative incidence of mortality estimated using the Kaplan-Meier method revealed significant differences among the three cohorts during the follow-up period (p<0.001). The cumulative incidence mortality rate was considerably higher in the PSE cohort than that in the PSN and comparison cohorts (Figure 1). Compared with the comparison cohort, the total stroke cohort (adjusted HR=2.12, 95% CI=2.04–2.20), PSE cohort (adjusted HR=4.18, 95% CI=3.91–4.48) and PSN cohort (adjusted HR=1.90, 95% CI=1.83–1.98) were associated with significantly higher risks of mortality. Among all study cohorts, the risk of mortality was higher in the patients aged ≥75 years (adjusted HR=5.07, 95% CI=4.78–5.38) and those aged 65–74 years (adjusted HR=2.29, 95% CI=2.15–2.43) than in those aged 40–-64 years. The risk of mortality was higher in male patients than in female patients. Among the comorbidities, alcohol-related illness (adjusted HR=1.30, 95% CI=1.17–1.45), COPD (adjusted HR=1.28, 95% CI=1.23–1.33), CAD (adjusted HR=1.10, 95% CI=1.05–1.14), diabetes (adjusted HR=1.64, 95% CI=1.57–1.71), hypertension (adjusted HR=1.10, 95% CI=1.03–1.17), asthma (adjusted HR=1.11, 95% CI=1.05–1.16), and cancer (including brain tumor) (adjusted HR=1.69, 95% CI=1.58–1.81) were risk factors associated with increased mortality. The other comorbidities were reciprocal factors for low mortality risk (Table 2).

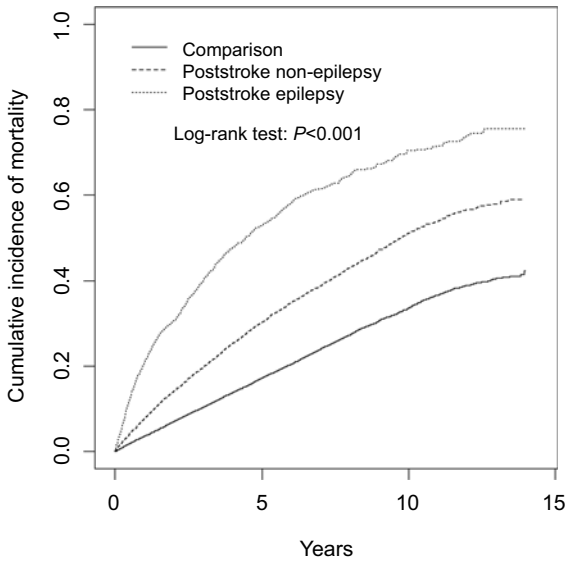

Figure 1 Comparison of cumulative incidence of mortality among the patients with poststroke epilepsy, patients with stroke without epilepsy, and comparisons from normal population.

Table 3 shows the comparison of mortality incidence and HRs measured using the Cox model among the post-stroke cohorts (PSE and PSN) and comparison cohort after stratification by age, sex, and comorbidities. The adjusted HRs of mortality in the PSE and PSN cohorts were all significantly higher than those of the comparison cohort in all age groups, both sexes, and irrespective of the presence of comorbidities (Table 3).

When we used the PSN cohort as the reference group and analyzed the age-specific mortality risk after stratification by age, the risks of mortality were significantly higher in the PSE cohort than in the PSN cohort among all the age groups. Similarly, the sex-specific mortality risk was significantly higher for both the sexes in the PSE cohort than in the PSN cohort. The mortality risk analyzed after stratification by comorbidities in the PSE cohort showed significantly high risks in patients in both strata (patients without comorbidities, adjusted HR=8.57, 95% CI=3.49–21.1; patients with any one of comorbidities, adjusted HR=2.21, 95% CI=2.06–2.37) (Table 4).

Discussion

The subsequent all-cause mortality risk in poststroke patients in Taiwan was approximately two times the likelihood in patients with PSE than those without (4.18 and 1.90, respectively, in adjusted HRs) and approximately four times higher than that in the normal population. Comparing to a similar study in a Western country in that the patients with remote structural epilepsy had 3.7 times of mortality rate,[12] our study revealed a considerably higher mortality risk in the Taiwanese patients with PSE. Additionally, although epilepsy could not be isolated from other factors in the study as in other like this, we still noticed that advanced age (≥65 years), male sex, alcohol-related illness, COPD, CAD, diabetes, hypertension, asthma, and cancer would further increase the mortality risk of patients. High mortality risks in patients with PSE were observed in both sexes, all age groups (>40 years), and irrespective of the presence of various comorbidities. Considering the sex differences in mortality risk, we learned that women have been reported to be more easily convinced than men to use additional medical services and spend money on health care.[16,17]

Table 2 Incidence and HR for mortality and associated risk factors

	Event (N)	Person-years	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)*
Stroke					
Comparison cohort	6,120	156,160	39.2	1.00	1.00
Poststroke non-epilepsy	4,199	58,806	71.4	1.82 (1.75, 1.89)	1.90 (1.83, 1.98)
Poststroke epilepsy	965	6,722	143.6	3.65 (3.41, 3.91)	4.18 (3.91, 4.48)
Total stroke	5,164	65,528	78.8	2.01 (1.93, 2.08)	2.12 (2.04, 2.20)
Age, year					
40–64	1,534	84,946	18.1	1.00	1.00
65–74	3,065	69,777	43.9	2.44 (2.29, 3.59)	2.29 (2.15, 2.43)
≥75	6,685	66,965	99.8	5.62 (5.31, 5.94)	5.07 (4.78, 5.38)
Sex					
Female	4,658	99,949	46.6	1.00	1.00
Male	6,626	121,740	54.4	1.17 (1.13, 1.21)	1.18 (1.13, 1.23)
Comorbidity					
Alcohol-related illness					
No	10,928	212,580	51.4	1.00	1.00
Yes	356	9,109	39.1	0.76 (0.68,0 0.84)	1.30 (1.17, 1.45)
Anxiety disorders					
No	8,564	155,907	54.9	1.00	1.00
Yes	2,720	65,782	41.4	0.75 (0.72, 0.78)	0.75 (0.71, 0.79)
Mental disorders					
No	4,968	99,244	50.1	1.00	1.00
Yes	6,316	122,445	51.6	1.03 (0.99, 1.07)	
Insomnia					
No	3,475	69,595	49.9	1.00	1.00
Yes	7,809	152,093	51.3	1.02 (0.98, 1.06)	
Depression					
No	10,383	199,901	51.9	1.00	1.00
Yes	901	21,788	41.4	0.79 (0.74, 0.85)	1.06 (0.99, 1.15)
Head injury					
No	10,982	212,362	51.7	1.00	1.00
Yes	302	9,327	32.4	0.63 (0.56, 0.70)	0.91 (0.81, 1.02)
COPD					
No	6,722	161,528	41.6	1.00	1.00
Yes	4,562	60,160	75.8	1.82 (1.75, 1.89)	1.28 (1.23, 1.33)
Coronary artery disease					
No	5,303	120,403	44.0	1.00	1.00
Yes	5,981	101,285	59.1	1.34 (1.29, 1.39)	1.10 (1.05, 1.14)

(*Continued*)

Table 2 (Continued).

	Event (N)	Person-years	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)*
Diabetes					
No	7,767	167,602	46.3	1.00	1.00
Yes	3,517	54,087	65.0	1.40 (1.35, 1.46)	1.64 (1.57, 1.71)
Hypertension					
No	1,068	27,513	38.8	1.00	1.00
Yes	10,216	194,176	52.6	1.35 (1.27, 1.44)	1.10 (1.03, 1.17)
Hyperlipidemia					
No	7,622	126,993	60.0	1.00	1.00
Yes	3,662	94,696	38.7	0.64 (0.62, 0.67)	0.64 (0.62, 0.67)
Asthma					
No	9,232	191,801	48.1	1.00	1.00
Yes	2,052	29,887	68.7	1.42 (1.36, 1.49)	1.11 (1.05, 1.16)
Cancer (including brain tumor)					
No	10,333	212,448	48.6	1.00	1.00
Yes	951	9,240	102.9	2.11 (1.97, 2.25)	1.69 (1.58, 1.81)

Notes: Rate, per 1,000 person-years; *variables found to be statistically significant in the univariable model were further included in the multivariable model.

This observation may explain the lower mortality risk in women than in men after a stroke event. Therefore, we suggested PSE as a contributory factor for increasing mortality in poststroke patients in Taiwan even when considered that there would be overlapping comorbidities in some cases or there would be concomitantly more PSE and higher mortality in some severe handicapped poststroke cases. All these conditions might reasonably lead to a higher risk of subsequent mortality in poststroke patients.

This cohort study revealed that 12.14% of poststroke patients would develop epilepsy and the incidence of PSE in Taiwan was higher than those (3.1–11.5%) reported in developed Western countries.[9–11] We consider that the different local findings in incidence and long-term mortality rate in patients with PSE are contributed from that we have progressively reduced acute mortality rate of stroke for 2 decades.[18] Stroke is currently the fourth leading mortality cause in Taiwan. The more survival patients after stroke events might cause more handicapped and comorbid ones in the society, and that could result more PSE patients and higher averaged long-term mortality rate in them. Furthermore, a recent study in the United States has revealed an interesting tendency of higher epilepsy-related death in Black and Asian population than in non-Hispanic White ones.[19] All of these may result a higher PSE incidence and its higher mortality rate in poststroke patients in Taiwan.

Epileptogenesis involves molecular and cellular alterations after a brain insult. It increases brain excitability and eventually enables the brain tissue to generate spontaneous recurrent seizures. Because we currently cannot reliably identify a patient with developing epileptogenesis and reverse it after a brain insult,[20,21] understanding the incidence, outcome risk, and treating correlated risk factors for PSE are practically beneficial for daily clinical practices other than to prevent epileptogenesis. Thus, according to our results, once a patient experiences a stroke event in Taiwan, PSE is considerably expected to play a more critical role than was previously thought in long-term care, and it affects long-term care more prominently than other factors do. PSE directly increases the care burden of families, societies, and the government. Additional studies in different countries are required to confirm whether this result is globally applicable.

In this study, we intentionally enrolled patients with both first-time and recurrent stroke events to estimate the correlation of subsequent PSE and poststroke inpatient all-cause mortality; we excluded cases of mortality occurring outside hospitals in this study. The NHI program, which is a universal mandatory insurance

Table 3 Comparison of incidence and HR for mortality stratified by age, sex, and comorbidity between poststroke and comparison cohorts

	Comparison cohort N=27,207		Poststroke								
			Total stroke (N=13,603)			Poststroke non-epilepsy (N=11,952)			Poststroke epilepsy (N=1,651)		
	Event (N)	Rate	Event (N)	Rate	Adjusted HR (95% CI)*	Event (N)	Rate	Adjusted HR (95% CI)*	Event (N)	Rate	Adjusted HR (95% CI)*
Age, years											
40–64	717	12.2	817	31.2	2.72 (2.46, 3.01)	604	26.2	2.32 (2.08, 2.58)	213	66.4	5.38 (4.61, 6.28)
65–74	1,526	31.1	1,539	74.6	2.50 (2.33, 2.69)	1,257	66.7	2.24 (2.08, 2.41)	282	157.4	5.28 (4.65, 6.00)
≥75	3,877	80.3	2,808	150.4	1.94 (1.85, 2.04)	2,338	138.0	1.79 (1.70, 1.88)	470	272.6	3.38 (3.07, 3.72)
P for interaction					<0.001			<0.001			
Sex											
Female	2,515	35.8	2,143	72.2	2.12 (2.00, 2.24)	1,751	65.3	1.91 (1.80, 2.04)	392	137.8	3.99 (3.59, 4.45)
Male	3,605	42.0	3,021	84.3	2.12 (2.02, 2.23)	2,448	76.6	1.90 (1.80, 2.00)	573	147.8	4.28 (3.91, 4.67)
P for interaction					0.90			0.40			
Comorbidity											
None	70	29.2	49	47.7	1.88 (1.31, 2.72)	43	43.0	1.69 (1.16, 2.47)	6	226.4	16.1 (6.79, 38.4)
With any one	6,050	39.4	5,115	79.3	2.08 (2.00, 2.16)	4,156	71.9	1.86 (1.79, 1.94)	959	143.2	4.20 (3.92, 4.49)
P for interaction					0.26			0.84			

Notes: Rate, per 1,000 person-years; *variables found to be statistically significant in the univariable model were further included in the multivariable model.

program, has been covering more than 99% of Taiwan's population for more than 20 years. The program guarantees residents of Taiwan equal access to medical service regardless of their socioeconomic status, background, and critical illness status.[13,22] Taiwan's universal health care system has resulted in relatively few disparities in access to inpatient services and ultimate outcomes between different hospitals and across different areas in Taiwan.[23,24] Therefore, the proportion of patients with stroke or PSE dying outside hospitals is low. However, the possibility of underestimation bias in the results should be considered.

Because this study included a nationwide, population-based sample with a relatively low risk of recall or selection bias, our findings are valuable for the clinicians and the NHI of Taiwan. Moreover, our results can be used as a reference for other developing Asian countries with a heritage similar to that of Taiwan. However, this study has several limitations. First, we could not directly contact the patients because their identities are anonymized in the NHIRD. Therefore, the study design did not include details regarding the type or severity score of their stroke events, the burden or severity of their epilepsy events, or how PSE was treated in the cohort. Second, although the NHI program performs thorough quarterly reviews to ensure that the files are accurate and that false claims are heavily penalized, rare occurrences of miscoding may have nevertheless

Table 4 Comparison of incidence and hazard ratio for mortality stratified by age, sex, and comorbidities between poststroke patients with and without epilepsy

	Poststroke non-epilepsy N=11,952	Poststroke epilepsy N=1,651
	Adjusted HR* (95% CI)	Adjusted HR* (95% CI)
All	1.00	2.13 (1.98, 2.29)
Age, years		
40–64	1.00	2.26 (1.93, 2.66)
65–74	1.00	2.33 (2.04, 2.65)
≥75	1.00	1.86 (1.68, 2.06)
Sex		
Female	1.00	2.06 (1.85, 2.31)
Male	1.00	2.16 (1.97, 2.36)
Comorbidity		
None	1.00	8.57 (3.49, 21.1)
With any one	1.00	2.21 (2.06, 2.37)

Notes: *Variables found to be statistically significant in the univariable model were further included in the multivariable model.

occurred in the NHIRD. Additionally, we could not ascertain whether poststroke mortality was directly caused by the stroke event itself, PSE, or other poststroke comorbidities. Finally, although our study design included adequate control of numerous confounding factors, unmeasured or unknown confounders may have generated a bias. However, after considering the aforementioned limitations, our results indicated that the sample size was sufficient to statistically demonstrate the high subsequent mortality risk in patients with PSE.

Conclusion

The mortality risk in patients with stroke is approximately two times the likelihood in those with PSE than in those without, and approximately four times higher than that in the normal population. Our findings provide vital information for clinicians and the government to improve the long-term survival of patients with stroke in the future.

Data sharing statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). Any researcher interested in accessing this dataset can submit an application form to the MOWH requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan MOHW address: No.488, Sec. 6, Zhongxiao E. Road, Nangang Dist.rict, Taipei City 115, Taiwan. Phone: +886 2-8590-6848.886

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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