Original Article

Poststroke Parkinsonism associates with an increased mortality risk in patients

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Background: To determine whether poststroke Parkinsonism (PSP) increases mortality risk in poststroke patients by using Taiwan National Health Insurance Research Database (NHIRD).

Methods: We analyzed NHIRD data of ≥40-year-old patients diagnosed as having stroke [International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes 430-438] between 2000 and 2013. Poststroke patients were divided into those with subsequent PSP (ICD-9-CM codes 332, 332.0, and 332.1) and without PSP (non-Parkinsonism, PSN) cohorts, all compared with a sex-, age-, comorbidity-, and index date-matched comparison cohort. We calculated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of all-cause mortality risk in these cohorts after adjustments for age, sex, and comorbidities.

Results: PSP was noted in 11.87% (1,644/13,846) of poststroke patients. In the PSN, PSP, and comparison cohorts, mortality incidence rates were 69.1, 124.9, and 38.8 per 1,000 person-years, respectively. Compared with the comparison cohort, the mortality risks in patients aged 40 to 64, 65 to 74, and ≥75 years were respectively 2.21-, 1.91-, and 1.86-fold higher mortality risks in the PSN cohort and 4.57-, 2.84-, and 2.27-fold higher mortality risks in the PSP cohort. Male sex further increased mortality risk in poststroke patients with PSP.

Conclusions: Long-term all-cause mortality risk is increased by 1.39 times in poststroke patients with PSP than in those without. Our findings depict vital information in incidence and risk of PSP. Those would aid clinicians and the government to improve future poststroke care.

Keywords: Cohort study; mortality; National Health Insurance; Parkinsonism; stroke

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Introduction

Stroke is the most well-known and globally prevalent severe neurovascular disease. Irrespective of whether stroke is ischemic or hemorrhagic, patients who survive the acute stage of stroke typically have various disabilities and comorbidities subsequently. Stroke is the most common cause of disability and dependence in adults and it reduces their quality of life (1-3). Patients with stroke frequently present with various types of involuntary movement disorders, such as chorea, tremor, dystonia, myoclonus, and Parkinsonism (4-7). These movement disorders may occur as part of the acute symptoms of stroke, or they may be delayed or even progressively develop as poststroke comorbidities. In a 56-patient series, Alarcon *et al.* reported that chorea is the most common movement disorder following stroke (8). Patients with poststroke Parkinsonism (PSP) usually present with persistent symptoms of bradykinesia, rest tremor, muscular rigidity, and postural instability in daily activity, and the broad-spectrum movement disabilities might further reduce rehabilitation efficacy and quality of life in poststroke patients.

Among various types of Parkinsonism syndromes, Parkinson disease (PD) is the primary one that occurs without a preceding neurological disease and is believed to be a neurodegenerative disorder that develops with aging. Several studies have examined risk and mortality in patients with PD, the primary Parkinsonism (9-11). However, insufficient data have been provided for mortality risk and related risk factors in patients with secondary Parkinsonism; it is also unclear whether PSP affects the long-term survival in poststroke patients. Therefore, we conducted this study and tried to clarify the relationship between stroke and PSP, and how much risk and burden would be increased by PSP after a stroke.

Further investigation to understand the association of mortality risk in patients with PSP and without PSP is warranted to establish future poststroke management strategies. Here, we used a nationwide population-based database to investigate and compare mortality risk and risk factors between Taiwanese patients with PSP and those without PSP [poststroke non-Parkinsonism (PSN)]. Because of the similar ethnic and cultural backgrounds in Taiwan and other Asian regions (12), the findings of this study might be useful for developing and implementing poststroke care strategies in Asian regions in addition to Taiwan.

Methods

Data source

The National Health Insurance Research Database (NHIRD) is maintained and released by Taiwan National Health Research Institutes (NHRI). The database contains all health and medical outpatient and inpatient treatment data of every insurant. Here, we used the Longitudinal Health Insurance Database 2000 (LHID2000), which contains the data of 1 million patients randomly selected from the NHIRD, and the distribution of age and sex is similar to that in the entire Taiwanese population. The patient identity is protected through data encryption by using identification numbers before the data are released for research. In addition, all diagnoses in the database are coded using International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Data availability statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan. Phone: +886-2-8590-6848. All relevant data are within the paper.

Study population

We enrolled 13,846 patients aged ≥40 years who received new stroke diagnoses (ICD-9-CM codes 430-438) between January 2000 and December 2013. The first diagnosis date was defined as the index date. The total stroke cohort was further divided into PSP and PSN cohorts according to whether the subsequent diagnosis of any type of Parkinsonism (ICD-9-CM codes 332, 332.0, and 332.1) was coded after stroke occurrence. A total of 1,644 patients developed Parkinsonism after stroke, and 12,202 patients did not. The comparison cohort (without stroke, without Parkinsonism) was matched by age, sex, and index year at a ratio of 1:1. In addition, we excluded stroke or non-stroke participants aged <40 years or those with a

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history of any type of Parkinsonism before the index date. Preexisting comorbidities for each patient were identified at baseline, including alcohol-related illness, anxiety disorders, mental disorders, insomnia, depression, head injury, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), diabetes mellitus, hypertension, hyperlipidemia, asthma, any cancer (including brain tumors), liver cirrhosis and end stage renal disease. Person-years were calculated from enrollment to death or last follow-up (31 December 2013), whichever occurred first.

Statistical analysis

Age, sex, and comorbidity distribution between the stroke and comparison cohorts, expressed as number and percentage, was tested using the chi-square test and *t*-test. To estimate the mortality risk in the PSP and PSN cohorts, hazard ratios (HRs), adjusted HRs (aHRs), and 95% confidence intervals (CIs) were calculated using crude and adjusted Cox proportional hazard models. The incidence rates (IRs) of mortality in the 2 cohorts were measured. Cumulative incidence curves of mortality were computed using the Kaplan–Meier method, and the differences between the PSN, PSP, and comparison cohorts were tested using the log-rank test. A multivariate Cox proportional hazard model was used to estimate the aHRs with adjustment for age, sex, and comorbidities, which significantly differed in the univariate model with and without comorbidities. Age-, sex-, and comorbidity-stratified analyses were performed for exploring the association of stroke and Parkinsonism with mortality among the specific populations.

All statistical analyses were performed on SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). Statistical significance was determined using 2-tailed tests at $P<0.05$.

Results

Baseline characteristics

Among 13,846 poststroke patients, 1,644 developed PSP. The total stroke, PSN, PSP, and comparison cohorts included respectively 33.1%, 35.9%, 12.8%, and 35.3% of patients aged 40 to 64 years; 30.6%, 30.2%, 33.7%, and 30.4% of patients aged 65 to 74 years; and 36.3%, 34.0%, 53.5%, and 34.3% of patients aged >75 years. The mean age of the total stroke, PSN, PSP, and comparison cohorts were 69.7, 69.0, 68.9, and 68.9 years, respectively. Women accounted for 43.5%, 43.3%, 43.5%, and 41.5% of the comparison, total stroke, PSN, and PSP cohorts, respectively. The comorbidities of head injury, COPD, CAD, and end stage renal disease significantly differed between the total stroke cohort and non-stroke cohort (P=0.001, 0.05, 0.02, and 0.001, respectively; *Table 1*).

Mortality rates in different stroke cohorts

According to the Kaplan-Meier plots, considerable differences were observed in the cumulative incidence of mortality among the non-stroke, PSN, and PSP cohorts (log-rank test, $P<0.001$). The PSP cohort had the highest cumulative incidence of mortality compared with the PSN and comparison cohort during the 14-year follow-up (*Figure 1*).

As listed in *Table 2*, the IRs of mortality for the total stroke, PSN, PSP, and comparison cohorts were 75.2, 69.1, 124.9, and 38.8 per 1,000 person-years. Moreover, the mortality risk increased with age: IRs of mortality in patients aged 40 to 64, 65 to 74, and ≥75 years were 21.5, 49.1, and 108.5 per 1,000 person-years. Compared with patients aged 40 to 64 years, those aged 65 to 74 years and ≥75 years had 2.16-and 4.80-fold higher mortality risk. Male patients had 1.28-fold higher mortality risk than did female patients. Furthermore, in the model with and without comorbidities, mortality risk was significantly higher in patients with alcohol-related illness (aHR =1.28), COPD (aHR =1.31), CAD (aHR =1.10), diabetes (aHR =1.65), hypertension (aHR =1.16), asthma (aHR =1.09), cancer (aHR =1.67), liver cirrhosis (aHR =1.67), and end stage renal disease (aHR =3.22) than in patients without any comorbidity. In addition, the mortality risk was lower in patients with anxiety disorder (aHR =0.75) and hyperlipidemia (aHR =0.67) than in patients without these comorbidities (*Table 2*).

Stratified analysis of PSP and mortality

A multivariable model was used to analyze the data of 13,846 poststroke patients. *Table 3* demonstrates compared with the comparison cohort, the mortality risks in patients aged 40 to 64, 65 to 74, and ≥75 years were respectively 2.32-, 2.02-, and 1.93-fold higher mortality risks in the total stroke cohort; 2.21-, 1.91-, and 1.86-fold higher mortality risks in the PSN cohort; and 4.57-, 2.84-, and 2.27-fold higher mortality risks in the PSP cohort. Moreover, compared with the comparison cohort, the total stroke,

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Table 1 Age, sex, and comorbidity distribution in all cohorts

Variable	Total stroke, N=13,846		Poststroke non-Parkinsonism, N=12,202		Poststroke Parkinsonism, N=1,644		Comparison cohort, N=13,846		P value[†]
	n	%	N	%	n	%	n	%	
Age, year									0.001
40–64	4,586	33.1	4,375	35.9	211	12.8	4,887	35.3	
65–74	4,236	30.6	3,682	30.2	554	33.7	4,215	30.4	
≥75	5,024	36.3	4,145	34.0	879	53.5	4,744	34.3	
Mean (SD)[§]	69.7	11.8	69.0	12.0	74.7	8.89	68.9	11.4	<0.001
Sex									0.66
Female	5,988	43.3	5,306	43.5	682	41.5	6,024	43.5	
Male	7,858	56.8	6,896	56.5	962	58.5	7,822	56.5	
Comorbidity									
Alcohol-related illness	805	5.81	736	6.03	69	4.20	846	6.11	0.30
Anxiety disorders	4,349	31.4	3,689	30.2	660	40.2	4,347	31.4	0.98
Mental disorders	7,885	57.0	6,677	54.7	1,208	73.5	7,787	56.2	0.23
Insomnia	9,912	71.6	8,579	70.3	1,333	81.1	9,931	71.7	0.80
Depression	1,562	11.3	1,275	10.5	287	17.5	1,589	11.5	0.61
Head injury	950	6.86	814	6.67	136	8.27	1,270	9.17	0.001
Chronic obstructive pulmonary disease	4,053	29.3	3,369	27.6	684	41.6	3,907	28.2	0.05
Coronary artery disease	6,578	47.5	5,661	46.4	917	55.8	6,391	46.2	0.02
Diabetes	3,722	26.9	3,251	26.6	471	28.7	3,446	24.9	0.08
Hypertension	12,115	87.5	10,597	86.9	1,518	92.3	12,060	87.1	0.32
Hyperlipidemia	6,148	44.4	5,456	44.7	692	42.1	6,076	43.9	0.38
Asthma	2,000	14.4	1,706	14.0	294	17.9	1,985	14.3	0.28
Cancer (including brain tumor)	638	4.61	567	4.65	71	4.32	698	5.04	0.09
Liver cirrhosis	454	3.28	388	3.18	66	4.01	431	3.11	0.43
End stage renal disease	364	2.63	327	2.68	37	2.25	150	1.08	0.001

[§], Chi-square test, *t*-test; [†], total stroke vs. comparison cohort.

PSN, and PSP cohorts demonstrated respectively 1.99-, 1.88-, and 2.81-fold higher mortality risks in female patients and 1.92-, 1.77-, and 3.02-fold higher mortality risks in male patients. Patients without any comorbidity in the total stroke, PSN, and PSP cohorts had 2.23-, 2.09-, and 6.46-fold higher mortality risks than did those in the comparison cohort, respectively, whereas those with any one comorbidity had 1.97-, 1.87-, and 2.55-fold higher mortality risks, respectively (*Table 3*).

Comparison between PSP and PSN cohorts

Compared with the PSN cohort, the PSP cohort had overall higher mortality risk (aHR =1.39). Patients aged 40 to 64, 65 to 74, and ≥75 years in the PSP cohort had 2.07-, 1.46-, and 1.28-fold higher mortality risks than did those

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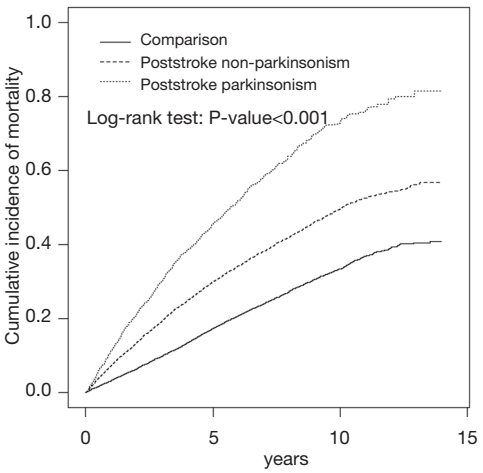

Figure 1 Comparison of cumulative incidence of mortality among patients with poststroke Parkinsonism, patients with stroke without Parkinsonism, and patients in the comparison cohort.

in the PSN cohort, respectively. Compared with the PSN cohort, female and male patients in the PSP cohort had 1.49- and 1.72-fold higher mortality risks. Patients without any and with any one comorbidity in the PSP cohort had 3.02- and 1.38-fold significantly higher mortality risks than did those in the PSN cohort (*Table 4*).

Discussion

In this study, 11.87% (1,644/13,846) of Taiwanese patients aged ≥40 years developed PSP after stroke during a 14-year follow-up. These patients had an overall mortality rate of 124.9 per 1,000 person-years, and patients with PSN had a mortality rate of 69.1 per 1,000 person-years. Compared with the reported mortality rate of 435.3 per 100,000 in the general population of Taiwan (13), mortality risk in PSP patients was much higher. Moreover, the patients with PSP would have increased all-cause mortality risk by about 1.39 times than those without PSP. Because Parkinsonism is a progressive neurodegenerative disorder, the cumulative incidence of PSP in patients newly diagnosed with stroke should reasonably increase gradually with their age and poststroke duration. Our results could not specifically categorize the subtypes of Parkinsonism in these patients and hardly compared with those of previous studies focused on different Parkinsonism and with limited follow-up duration (8,14,15). However, a study in 1,500 poststroke patients with 1 to 3-year follow-up revealed a 3.7% rate of developing poststroke movement disorders (8). Our study demonstrated a higher incidence of developing PSP in long-term follow-up, and PSP could be considered a specific predictor of poor long-term survival outcomes in poststroke patients.

The predisposing or risk factors for PSP remain unclear because the mechanism of secondary Parkinsonism development is more complicated than that of PD- whereby PD may be associated with various brain insults, such as exposure to pesticides (16,17). In vascular Parkinsonism, another Parkinsonism type, vascular lesions potentially disrupt the connections between the basal ganglia, thalamus, and motor cortex, leading to sensorimotor integration between the cortex, subcortical white matter, and brain stem (7,18-20). Our patients with PSP would be categorized as belonging to the group with vascular Parkinsonism, with similar pathogenesis for Parkinsonism. However, we found some further information of PSP in this study. Although the cumulative incidence of mortality in the PSP cohort would progressively increase with time, male poststroke patients and those aged <65 years would be at a much higher risk of mortality if they develop PSP.

In this study, we further analyzed the interaction effects of various comorbidities, including alcohol-related illness, anxiety disorders, mental disorders, insomnia, depression, head injury, COPD, CAD, diabetes, hypertension, hyperlipidemia, asthma, any cancer (including brain tumors), liver cirrhosis and end stage renal disease, with PSP on poststroke mortality risk. Compared with the PSN cohort, patients without any of these comorbidities in the PSP cohort had a higher risk than did those with one or more of these comorbidities. To the best of our knowledge, this is the first large-scale study to document the negative effect of PSP on long-term survival outcomes in poststroke patients. The awareness of incidence and risk of PSP may aid in the future development and implementation of advanced strategies for poststroke care in Taiwan. It is a unique advantage to have big health database available for planning, designing and executing clinical trials. With the big health database available, feasibility survey of a new trial can be assessed to identify the appropriate hospitals with adequate patient populations, reasonable length of hospital stay and therapeutic outcomes to identify the appropriate clinical trial sites for joining the multicenter clinical trials. Based on our results, more similar studies could be conducted in different societies or medical care systems to test whether our findings are globally applicable.

In this study, we enrolled all patients with first-ever

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Table 2 Incidence and hazard ratio of mortality and associated risk factors

Variable	Event (N)	Person-years	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)[&]
Stroke					
Comparison cohort	3,036	78,198	38.8	1.00	1.00
Poststroke non-Parkinsonism	4,133	59,810	69.1	1.94 (1.85, 2.03)***	1.86 (1.77, 1.95)***
Poststroke Parkinsonism	914	7,317	124.9	1.78 (1.70, 1.87)***	2.54 (2.36, 2.74)***
Total stroke	5,047	67,128	75.2	3.22 (2.99, 3.47)***	1.95 (1.87, 2.04)***
Age, year					
40–64	1,211	56,417	21.5	1.00	1.00
65–74	2,296	46,742	49.1	2.30 (2.14, 2.46)***	2.16 (2.01, 2.31)***
≥75	4,576	42,166	108.5	5.14 (4.82, 5.48)***	4.80 (4.49, 5.14)***
Sex					
Female	3,179	64,820	49.0	1.00	1.00
Male	4,904	80,505	60.9	1.24 (1.19, 1.30)***	1.28 (1.22, 1.34)***
Comorbidity					
Alcohol-related illness					
No	7,730	138,010	56.0	1.00	1.00
Yes	353	7,316	48.3	0.86 (0.77, 0.96)**	1.28 (1.15, 1.43)***
Anxiety disorders					
No	6,063	100,784	60.2	1.00	1.00
Yes	2,020	44,542	45.4	0.75 (0.72, 0.79)***	0.75 (0.71, 0.79)***
Mental disorders					
No	3,473	63,814	54.4	1.00	1.00
Yes	4,610	81,511	56.6	1.04 (0.99, 1.08)	
Insomnia					
No	2,539	45,689	55.6	1.00	1.00
Yes	5,544	99,636	55.6	1.00 (0.95, 1.04)	
Depression					
No	7,352	129,337	56.8	1.00	1.00
Yes	731	15,988	45.7	0.80 (0.74, 0.87)***	1.06 (0.97, 1.15)
Head injury					
No	7,583	134,867	56.2	1.00	1.00
Yes	500	10,459	47.8	0.85 (0.78, 0.93)***	1.06 (0.97, 1.16)
Chronic obstructive pulmonary disease					
No	4,953	107,841	45.9	1.00	1.00
Yes	3,130	37,485	83.5	1.82 (1.74, 1.90)***	1.31 (1.25, 1.38)***

Table 2 (*Continued*)

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Table 2 (*Continued*)

Variable	Event (N)	Person-years	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)[&]
Coronary artery disease					
No	3,763	79,015	47.6	1.00	1.00
Yes	4,320	66,310	65.2	1.37 (1.31, 1.43)***	1.10 (1.05, 1.15)***
Diabetes					
No	5,485	109,683	50.0	1.00	1.00
Yes	2,598	35,642	72.9	1.46 (1.39, 1.53)***	1.65 (1.57, 1.73)***
Hypertension					
No	725	19,309	37.6	1.00	1.00
Yes	7,358	126,017	58.4	1.55 (1.44, 1.68)***	1.16 (1.07, 1.25)***
Hyperlipidemia					
No	5,384	83,133	64.8	1.00	1.00
Yes	2,699	62,192	43.4	0.67 (0.64, 0.70)***	0.67 (0.64, 0.70)***
Asthma					
No	6,693	126,432	52.9	1.00	1.00
Yes	1,390	18,893	73.6	1.39 (1.31, 1.47)***	1.09 (1.02, 1.16)**
Cancer (including brain tumor)					
No	7,533	140,069	53.8	1.00	1.00
Yes	550	5,256	104.6	1.94 (1.78, 2.12)***	1.67 (1.53, 1.82)***
Liver cirrhosis					
No	7,686	141,744	54.2	1.00	1.00
Yes	397	3,581	110.9	2.05 (1.85, 2.26)***	1.67 (1.51, 1.85)***
End stage renal disease					
No	7,784	143,690	54.2	1.00	1.00
Yes	299	1,635	182.8	3.38 (3.01, 3.79)***	3.22 (2.86, 3.62)***

Rate, per 1,000 person-years. [&], variables found to be statistically significant in the univariable model were further included in the multivariable model; **, P<0.01; ***, P<0.001. HR, relative hazard ratio; CI, confidence interval.

stroke or recurrent stroke to analyze the possible correlation of PSP with the poststroke long-term all-cause mortality. We did not intentionally exclude or identify patients with recurrent stroke because we estimated that 25% to 30% patients in the total stroke cohort would eventually have recurrent stroke (21), and that an annual stroke recurrence rate of approximately 3% is expected after the first episode (22). These data imply that stroke recurrence is an unavoidable natural progression of the disease, and stroke recurrence cannot be adjusted for. However, this study has several limitations and unadjusted biases. First, patients' identities are anonymized in the NHIRD to prevent researchers from directly contacting them. Therefore, we could not control all of the risk factors, such as alcohol drinking, smoking, and several socioeconomic factors. For the same reason, this study did not include the risk score of stroke and Parkinsonism, the type and clinical severity of stroke and Parkinsonism, the psychological burden, or treatment applied for PSP in the cohorts. Type of stroke is known to associate with development of Parkinsonism but it is hard to interpret the joint effects between the type of stroke, age, and detailed medical conditions in this study.

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Table 3 Comparison of incidence and hazard ratio of mortality stratified by age, sex, and comorbidities between poststroke and comparison cohorts

Variable	Comparison cohort, N=13,846		Poststroke								
			Total stroke, N=13,846			Poststroke non-Parkinsonism, N=12,202			Poststroke Parkinsonism, N=1,644		
	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, year											
40–64	387	13.0	824	31.0	2.32 (2.06, 2.62)***	741	29.2	2.21 (1.95, 2.50)***	83	68.0	4.57 (3.59, 5.82)***
65–74	833	33.2	1,463	67.6	2.02 (1.86, 2.21)***	1,203	63.8	1.91 (1.74, 2.08)***	260	93.3	2.84 (2.46, 3.26)***
≥75	1,816	78.0	2,760	146.1	1.93 (1.82, 2.05)***	2,189	140.5	1.86 (1.74, 1.98)***	571	172.6	2.27 (2.06, 2.50)***
P for interaction					<0.001			<0.001			
Sex											
Female	1,166	33.4	2,013	67.3	1.99 (1.85, 2.14)***	1,680	63.0	1.88 (1.74, 2.02)***	333	101.8	2.81 (2.48, 3.18)***
Male	1,870	43.2	3,034	81.6	1.92 (1.81, 2.04)***	2,453	74.0	1.77 (1.66, 1.88)***	581	143.6	3.02 (2.75, 3.32)***
P for interaction					0.17			0.40			
Comorbidity											
None	32	19.8	52	41.7	2.23 (1.43, 3.47)***	47	38.5	2.09 (1.33, 3.27)**	5	194.0	6.46 (2.49, 16.7)***
With any one	3,004	39.2	4,995	75.8	1.97 (1.88, 2.06)***	4,086	69.7	1.87 (1.79, 1.96)***	909	124.7	2.55 (2.37, 2.75)***
P for interaction					0.71			0.20			

Rate, per 1,000 person-years. [&], variables found to be statistically significant in the univariable model were further included in the multivariable model; **, P<0.01; ***, P<0.001. HR, relative hazard ratio; CI, confidence interval.

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

Variable	Adjusted HR[&] (95% CI)	
	Poststroke non-Parkinsonism, N=11,952	Poststroke Parkinsonism, N=1,651
All	1.00	1.39 (1.29, 1.49)***
Age, year		
40–64	1.00	2.07 (1.64, 2.61)***
65–74	1.00	1.46 (1.27, 1.67)***
≥75	1.00	1.28 (1.16, 1.40)***
Sex		
Female	1.00	1.49 (1.33, 1.68)***
Male	1.00	1.72 (1.57, 1.88)***
Comorbidity		
None	1.00	3.02 (1.19, 7.68)*
With any one	1.00	1.38 (1.29, 1.49)***

Rate, per 1,000 person-years. [&], variables found to be statistically significant in the univariable model were further included in the multivariable model; *, P<0.05; ***, P<0.001. HR, relative hazard ratio; CI, confidence interval.

Second, rare instances of miscoding may occur in a study with ICD-9-CM coding system, nevertheless the NHRI performs thorough quarterly reviews and false claims are heavily penalized to ensure that the data are accurate. Lack of biochemical measures and results of clinical examinations are also limitations in such kind of study design. Therefore, we could not determine whether any poststroke mortality in our cohort was caused by severe disability resulting from the stroke event, directly or indirectly caused by PSP or other diseases. Finally, although our study design included and was adjusted for numerous confounders, unmeasured or unknown confounders may have generated biases. However, after considering the aforementioned limitations and our results, this study sufficiently demonstrated statistically high subsequent all-cause mortality risk in patients with PSP compared with those without.

Conclusions

A total of 11.87% of Taiwanese patients aged ≥40 years would develop Parkinsonism after a stroke and these patients with PSP would have increased all-cause mortality risk by 1.39 times than those without PSP. There is a higher incidence of developing PSP than we thought before. As a secondary Parkinsonism, PSP could be considered a specific predictor of poor long-term survival outcomes in poststroke patients. Our findings provide vital information for clinicians and the government to improve poststroke care in the future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.90). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information,

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including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR4). The IRB also specifically waived the consent requirement.

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