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Risk of Stroke in Patients With Spontaneous Pneumothorax

A Nationwide, Population-Based Study

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Abstract: The association between spontaneous pneumothorax (SP) and stroke has not been reported, and this study aimed to explore this association. We used the National Health Insurance Research Database for conducting a nationwide, population-based, retrospective cohort study of patients newly hospitalized for SP from 2000 to 2010. A total of 2541 patients with newly diagnosed SP were included and compared with patients without SP. We observed that patients with SP were at higher risk for developing stroke, with an adjusted hazard ratio (HR) of 1.56. In addition, these patients had a significantly higher risk of hemorrhagic stroke (adjusted HR = 2.22) than of ischemic stroke (adjusted HR = 1.48). The risk of stroke was the highest in the initial 4 months after hospitalization for SP (adjusted HR = 3.41, 95% confidence interval = 1.98–5.87). In conclusion, our study revealed a correlation between stroke and a history of SP, and the risk of stroke after SP was time sensitive.

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Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, RCIPD = Registry for Catastrophic Illness Patient Database, SP = spontaneous pneumothorax.

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INTRODUCTION

Stroke is a major cause of morbidity and disability as well as the most common cause of cardiovascular death worldwide.[1] Moreover, stroke has been the 3rd leading cause of death in developed countries since 1990.[2,3] Annually, stroke causes approximately 5.5 million deaths. According to the Taiwan Ministry of Health and Welfare, stroke is also the 3rd leading cause of death in Taiwan. Risk factors for stroke include diabetes mellitus, hypertension, hyperlipidemia, arrhythmia, smoking, low physical activity, and inflammation.[4–7]

Spontaneous pneumothorax (SP) occurs when air leaks into the pleural space. Stroke and SP may share some risk factors, such as smoking and physical inactivity. Inflammatory cytokine levels are thought to be elevated in both diseases.[5,6] However, an association between SP and stroke has not been reported. In this study, we used Taiwan's National Health Insurance Research Database (NHIRD) for evaluating the aforementioned association.

METHODS

Data Source

The National Health Insurance (NHI) program, a universal health program, was established in Taiwan in 1995 and covered 99% of Taiwan's 23.72 million residents by 2009.[8] For research purposes, the National Health Research Institutes (NHRI) compiles all medical claims in the NHI program and annually releases the information to the public. The NHIRD contains comprehensive information regarding clinical visits, including details of medical orders; procedures; and medical diagnoses on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. To protect the privacy of all registered patients, the NHRI encrypts and converts the identification numbers of all NHIRD records before releasing them to researchers. 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 (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Patients

A retrospective cohort study was conducted on patients newly hospitalized for SP (ICD-9-CM 512.0) from 2000 to 2010. The date of the first hospitalization for SP was considered the index date. Patients with a history of stroke (ICD-9-CM 430–438) before the index date, age < 20 years, or with incomplete information in the database were excluded. For the non-SP

cohort, controls were randomly selected in a 4:1 ratio and frequency-matched with patients in the SP cohort with respect to age (5-year intervals), sex, and index date. A total of 2541 patients with SP and 10,164 patients without SP were followed until a diagnosis of stroke; loss to follow-up; withdrawal from the NHI program; or December 31, 2011, whichever occurred first.

Comorbidities

Inpatient diagnosis files were used for evaluating the presence of baseline comorbidities, including diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272), coronary artery disease (ICD-9-CM 410–414), acute myocardial infarction (ICD-9-CM 410), congestive heart failure (ICD-9-CM 428), atrial fibrillation (ICD-9-CM 427.31 and 427.32), cancer (ICD-9-CM 140–208), and chronic obstructive pulmonary disease (ICD-9-CM 490, 491 and 496).

Statistical Analysis

The chi-squared test was employed for evaluating and comparing the distribution of age, sex, and comorbidities between the SP and non-SP cohorts. Furthermore, the Student *t* test was used for examining the mean age and follow-up duration of both cohorts. The relative risk of stroke in the SP cohort, compared with that in the non-SP cohort, was analyzed using a univariate and multivariate Cox proportional hazards regression model. The multivariate model was adjusted for age, sex, and comorbidities. For each SP subject, we calculated the average admission number as following: the total number of the SP-related admissions during the entire study period divided by the number of follow-up years. Patients were then classified into 2 subgroups, ≤ 1 and ≥ 2 times, according to their mean number of annual SP-related hospitalization. All analyses were performed using SAS statistical software (Version 9.3 for Windows; SAS Institute, Inc., Cary, NC). A 2-tailed *P* value of <0.05 was considered significant.

RESULTS

The baseline characteristics of the SP and non-SP cohorts are displayed in Table 1. Most patients were age ≥ 65 years (45.4% in both cohorts). The mean age of patients in the SP and non-SP cohorts was 56.3 (± 22.5) and 55.7 (± 22.3) years, respectively. Men accounted for approximately 80.1% of all patients in both cohorts. Comorbidities were more prevalent in the SP cohort than in the non-SP cohort (all $P < 0.001$). Moreover, the average follow-up duration was 3.10 and 5.63 years for the SP and non-SP cohorts, respectively. Overall, the incidence of stroke in the SP and non-SP cohorts was 12.3 and 13.0 per 1000 person-years, respectively (Table 2). After adjustment for age, sex, and comorbidities, the risk of stroke was significantly higher in the SP cohort (adjusted hazard ratio [HR] = 1.57; 95% confidence interval [CI] = 1.25–2.00) than in the non-SP cohort. Compared with the non-SP cohort, the SP cohort was at a higher risk of hemorrhagic stroke (adjusted HR = 2.69, 95% CI = 1.47–4.93) than of ischemic stroke (adjusted HR = 1.46, 95% CI = 1.13–1.89); women were more affected than men. The adjusted HRs for stroke in the SP cohort

TABLE 1. Characteristics of Patients With Spontaneous Pneumothorax and Matched Patients Without Spontaneous Pneumothorax

	Spontaneous Pneumothorax				
	Yes (N = 2541)		No (N = 10,164)		
	n	%	n	%	*P* Value
Age, y					0.99
20–34	665	(26.2)	2660	(26.2)	
35–49	358	(14.1)	1432	(14.1)	
50–64	364	(14.3)	1456	(14.3)	
≥65	1154	(45.4)	4616	(45.4)	
Mean (SD)*	56.3	(22.5)	55.7	(22.3)	0.22
Sex					0.99
Female	507	(20.0)	2028	(20.0)	
Male	2034	(80.1)	8136	(80.1)	
Comorbidity					
Diabetes	356	(14.0)	516	(5.08)	<0.001
Hypertension	558	(22.0)	1044	(10.3)	<0.001
Hyperlipidemia	85	(3.35)	179	(1.76)	<0.001
Coronary artery disease	306	(12.0)	541	(5.32)	<0.001
Acute myocardial infarction	59	(2.32)	112	(1.10)	<0.001
Congestive heart failure	233	(9.17)	181	(1.78)	<0.001
Atrial fibrillation	101	(3.97)	90	(0.89)	<0.001
Cancer	274	(10.8)	328	(3.23)	<0.001
Chronic obstructive pulmonary disease	797	(31.4)	375	(3.69)	<0.001

Chi-squared test.
SD = standard deviation.
*T test.

TABLE 2. Incidence and HR of Stroke Between Patients With Spontaneous Pneumothorax and Without Spontaneous Pneumothorax

	Spontaneous Pneumothorax							
	Yes			No				
Outcome	Event	PY	Rate†	Event	PY	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
All	97	7876	12.30	742	57,256	13.00	0.95 (0.82, 1.10)	1.57 (1.25, 2.00)***
Hemorrhagic stroke	15		1.90	92		1.61	1.18 (1.00, 1.40)*	2.69 (1.47, 4.93)**
Ischemic stroke	82		10.40	650		11.40	0.92 (0.79, 1.07)	1.46 (1.13, 1.89)**
Sex								
Female	17	1436	11.80	124	11,522	10.80	1.10 (0.79, 1.53)	2.31 (1.29, 4.12)**
Male	80	6442	12.40	618	45,734	13.50	0.92 (0.78, 1.08)	1.48 (1.14, 1.92)**
Age, y								
≤49	9	5278	1.71	24	25,212	0.95	1.79 (1.46, 2.20)***	1.21 (0.51, 2.83)
50–64	16	990	16.20	77	9057	8.50	1.90 (1.37, 2.63)***	1.64 (0.85, 3.18)
≥65	72	1610	44.70	641	22,988	27.90	1.60 (1.31, 1.96)***	1.35 (1.03, 1.77)*
Comorbidity§								
No	24	5602	4.28	481	49,508	9.72	0.44 (0.34, 0.57)***	1.38 (0.91, 2.09)
Yes	73	2277	32.10	261	7748	33.70	0.95 (0.78, 1.16)	1.34 (1.02, 1.76)*
Chronic obstructive pulmonary disease								
No	50	6413	7.80	691	55,876	12.40	0.63 (0.52, 0.77)***	1.57 (1.17, 2.11)**
Yes	47	1465	32.10	51	1381	36.90	0.87 (0.65, 1.16)	1.26 (0.82, 1.93)

CI = confidence interval, HR = hazard ratio, PY = person-years.

†Incidence rate per 1000 PY.

‡Hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, acute myocardial infarction, congestive heart failure, atrial fibrillation, cancer, and chronic obstructive pulmonary disease.

§Patients with any 1 of the comorbidities (including diabetes, hypertension, hyperlipidemia, coronary artery disease, acute myocardial infarction, congestive heart failure, atrial fibrillation, cancer, and chronic obstructive pulmonary disease) were classified as the comorbidity group.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

were 2.31 (95% CI = 1.29–4.12) and 1.48 (95% CI = 1.14–1.92) in women and men, respectively. The age-specific stroke incidence increased with age in both cohorts. Compared with patients in the non-SP cohort, the risk of stroke was highest in patients with SP and age ≥65 years (adjusted HR = 1.35, 95% CI = 1.03–1.77). SP patients without chronic obstructive pulmonary disease had 1.57-fold higher risk of developing stroke than non-SP subjects (95% CI = 1.17–2.11). Compared with women without SP, men with SP had a higher risk of stroke (adjusted HR = 2.14, 95% CI = 1.58–2.92; Table 3). Moreover, compared with patients without SP and age ≤49 years, those with SP and age ≥65 years were 34.4-fold more likely to develop stroke (95% CI = 21.2–55.7), followed by those without SP and age ≥65 years (adjusted HR = 25.6, 95% CI = 17.0–38.6). Furthermore, compared with patients in the non-SP cohort without comorbidities, patients in the SP cohort with comorbidities had a higher risk of stroke (adjusted HR = 2.29, 95% CI = 1.78–2.94) than those with comorbidities alone or SP alone. Table 4 presents the comparison of the stroke risk stratified by the follow-up duration. The adjusted HR of stroke decreased with the increasing follow-up duration; patients in the SP cohort followed for ≤4 months were associated with the highest risk of stroke (adjusted HR = 3.75, 95% CI = 2.04–6.89), followed by those who were followed for 5 to 12 months (adjusted HR = 2.11, 95% CI = 1.20–3.70). Table 5 shows the stroke risks related to SP severity. Compared with patients in the non-SP cohort, patients with SP who were hospitalized more than twice per year had an adjusted HR of 28.1 for stroke (95% CI = 8.09–97.70).

DISCUSSION

As per our review of relevant literature, this is the first nationwide, population-based study investigating the association between stroke and SP. A total of 2541 patients with newly diagnosed SP were included and compared with patients without SP. We observed that the SP cohort had a higher risk of stroke, with an adjusted HR of 1.57, and the risk of hemorrhagic stroke (adjusted HR = 2.69) was higher than that of ischemic stroke (adjusted HR = 1.46).

Previous studies have demonstrated that SP causes lung atelectasis and hypoxemia.[9,10] Hypoxia is known to induce an inflammatory response in immune and endothelial cells through hypoxia signaling pathways.[11,12] Levels of interleukin-6, C-reactive protein, and tumor necrosis factor-α have been demonstrated to markedly increase under acute hypoxia.[13,14] Furthermore, increased serum levels of cytokines and accumulation of inflammatory cells are known to occur after a short-term exposure to hypoxic conditions.[12,15,16] Inflammation may play a crucial role in stroke occurrence, and studies have reported that inflammation induces vasculopathy, platelet activation, and thrombosis formation.[17,18]

TABLE 3. Cox Proportional Hazard Regression Analysis for the Risk of Stroke-Associated Spontaneous Pneumothorax With Interaction of Gender, Age, and Comorbidity

Variables		Adjusted HR[†] (95% CI)	*P* Value
Spontaneous pneumothorax	Sex		0.540
No	Female	1.00 (Reference)	
No	Male	1.41 (1.16, 1.71)**	
Yes	Female	1.88 (1.12, 3.17)*	
Yes	Male	2.14 (1.58, 2.92)**	
Spontaneous pneumothorax	Age, y		0.950
No	≤49	1.00 (Reference)	
No	50–64	8.50 (5.37, 13.40)**	
No	≥65	25.60 (17.00, 38.60)**	
Yes	≤49	1.75 (0.82, 3.77)	
Yes	50–64	14.20 (7.50, 27.00)**	
Yes	≥65	34.40 (21.20, 55.70)**	
Spontaneous pneumothorax	Comorbidity[‡]		<0.001
No	No	1.00 (Reference)	
No	Yes	1.49 (1.27, 1.74)**	
Yes	No	1.25 (0.83, 1.90)	
Yes	Yes	2.29 (1.78, 2.94)**	

CI = confidence interval, HR = hazard ratio.

[†]Hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, acute myocardial infarction, congestive heart failure, atrial fibrillation, cancer, and chronic obstructive pulmonary disease.

[‡]Patients with any 1 of the comorbidities (including diabetes, hypertension, hyperlipidemia, coronary artery disease, acute myocardial infarction, congestive heart failure, atrial fibrillation, cancer, and chronic obstructive pulmonary disease) were classified as the comorbidity group.

*$P < 0.050$.

**$P < 0.001$.

Smoking is a known risk factor for both SP and stroke. The risk of SP is strongly associated with the level of cigarette smoking.[19] Smoking-related small airway disease may contribute to the development of subpleural blebs and cause SP. In a prospective Swedish cohort study, smokers were 3.21 times more likely to develop stroke.[20] In the INTERSTROKE study, cigarette smoking was associated with a significantly increased risk of stroke (odds ratio, 2.09). However, the risk of ischemic stroke was stronger than that of hemorrhagic stroke (2.32 vs 1.45).[4]

Primary spontaneous pneumothorax generally occurs while a patient is at rest and is uncommon during exercise.[21] Low physical activity was associated with an increased risk of stroke in the NHANES I Epidemiologic Follow-up Study.[22] Chomistek et al[23] reported that prolonged sitting was associated with an increased risk of cardiovascular diseases. However, data on cigarette smoking and physical inactivity could not be retrieved from the NHIRD. A prospective cohort study design in the future can eliminate the confounding effect of smoking and low physical activity.

Stroke incidence increases with age and is likely to be high in an aging population. Thus, we selected age-matched controls to reduce the effect of age in our analysis. The present findings reveal a higher risk of stroke in patients with SP and age ≥65

TABLE 4. Trends of Stroke Event Risks by Stratified Follow-Up Years

	Spontaneous Pneumothorax							
	Yes			No				
Follow Time, mo	Event	PY	Rate[†]	Event	PY	Rate[†]	Crude HR (95% CI)	Adjusted HR[‡] (95% CI)
≤4	23	478	48.1	38	2525	15.1	3.20 (2.82, 3.62)**	3.75 (2.04, 6.89)**
5–12	20	1109	18.0	87	7409	11.7	1.54 (1.31, 1.80)**	2.11 (1.20, 3.70)*
>12	54	6292	8.58	617	47,322	13.0	0.66 (0.55, 0.79)**	1.22 (0.90, 1.65)

CI = confidence interval, HR = hazard ratio, PY = person-years.

[†]Incidence rate per 1000 PY.

[‡]Hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, acute myocardial infarction, congestive heart failure, atrial fibrillation, cancer, and chronic obstructive pulmonary disease.

*$P < 0.010$.

**$P < 0.001$.

TABLE 5. Risk of Stroke Among Frequency for Admissions Visits of Spontaneous Pneumothorax in Cox Proportional Hazard Regression

Number of Admissions per y	Event	PY	Rate[†]	Crude HR (95% CI)	Adjusted HR[‡] (95% CI)
None-spontaneous pneumothorax	742	57,256	13.0	1.00 (Reference)	1.00 (Reference)
Spontaneous pneumothorax					
≤1	93	7868	11.8	0.91 (0.73, 1.12)	1.53 (1.20, 1.94)[*]
≥2	4	11	369.3	45.90 (13.30, 158.20)[*]	28.10 (8.09, 97.70)[*]

CI = confidence interval, HR = hazard ratio, PY = person-years.
[†]Incidence rate per 1000 PY.
[‡]Hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, acute myocardial infarction, congestive heart failure, atrial fibrillation, cancer, and chronic obstructive pulmonary disease.
[*]$P < 0.001$.

years than in younger patients with SP. Several chronic diseases, such as diabetes, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, and cancer, are also associated with stroke.[4] Our results revealed that patients with SP and comorbidities had a higher risk of stroke than did patients without comorbidities. However, after controlling for comorbidities, the stroke risk remained higher in patients with SP. Moreover, this study revealed that the risk of stroke after SP diagnosis decreased with time. The stroke risk was the highest during the first 4 months after hospitalization for SP (adjusted HR = 3.75, 95% CI = 2.04–6.89); the adjusted HR of stroke decreased with increasing follow-up duration.

To our knowledge, this study is the first to investigate the association between SP and stroke. The strength of this study is the large sample size drawn from the NHIRD, providing adequate statistical power to detect an association between SP and stroke. Furthermore, the study groups were developed according to inpatient rather than outpatient claims, thus increasing the accuracy of SP diagnosis.

The present study had some limitations. First, factors associated with lifestyle, such as physical activity, dietary habits, alcohol use, cigarette smoking, and family history, can be related to stroke. However, information on these factors could not be retrieved from the NHIRD, and their association with SP remains unclear. To minimize the influence of smoking, we adjusted smoking-related diseases (including chronic obstructive pulmonary disease and coronary artery disease) in analysis. Second, stroke is a heterogeneous disease with many subtypes, including small vascular occlusion, cardioembolisms, and cryptogenic stroke.[24] In our study, stroke was only classified as hemorrhagic stroke and ischemic stroke. The association between SP and stroke subtypes could not be investigated precisely because of coding limitations.

In conclusion, our study revealed an increased risk of stroke after SP, and the risk was time sensitive. The stroke risk was higher in the initial 4 months after SP diagnosis. Therefore, awareness of the risk of stroke in patients with SP is crucial for both patients and physicians. Further studies are required for clarifying the pathophysiological mechanisms underlying the association between stroke and SP.

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