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The association between benzodiazepine use and pneumonia risk among patients with stroke: A population-based cohort study

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Abstract

Objectives

To investigate the association between benzodiazepine (BZD) use and the risk of pneumonia after stroke.

Design

Population-based propensity-matched retrospective cohort study.

Setting

Taiwan's National Health Insurance Research Database.

Participants

Patients newly diagnosed with stroke between 2000 and 2012 were identified and, after propensity score matching, 7602 patients were enrolled. Among these, 3801 patients received BZDs after stroke while 3801 did not.

Outcome measures

Hazard ratios (HRs) for developing pneumonia after stroke according to BZD use were assessed using Cox proportional hazards regression models. Analyses according to cumulative defined daily doses (cDDDs) of BZDs and stratification for age and sex were also performed.

Results

During a mean follow-up time of 4.4 years, 1218 patients in the BZD cohort and 526 patients in the non-BZD cohort developed pneumonia post-stroke. Patients using BZDs after stroke had a higher pneumonia risk than did those not using BZDs (63.9 vs. 35.9 per 1000 person-years, adjusted HR [aHR] = 2.33, 95% confidence interval [CI] = 2.09–2.59, $p < 0.001$). Analyses based on cumulative BZD dose revealed that all BZD user subgroups were associated with a higher risk of post-stroke pneumonia. The aHRs for patients taking 1–90, 91–365, and >365 cDDDs of BZDs were 2.26 (95% CI = 2.01–2.53; $p < 0.001$), 2.47 (95% CI = 2.12–2.87; $p < 0.001$), and 2.52 (95% CI = 2.13–2.99; $p < 0.001$), respectively. The significant association between BZD use and increased pneumonia risk persisted even after

stratifying subgroups by age and sex.

Conclusions

BZD use is associated with an increased risk of post-stroke pneumonia.

Strengths and limitations of this study

- This retrospective cohort study was performed based on a nationwide population database, which contained one million subjects randomly sampled from Taiwan's population.
- This is the first large-scale study to demonstrate an association between benzodiazepine use and pneumonia risk in patients post-stroke over a long-term follow-up period.
- The claim-based data did not allow for the retrieval of certain clinical information (e.g., patient lifestyle and physical, psychiatric, or laboratory examination data), and thus we could not control or adjust for these potential confounders in our analyses.

Introduction

Pneumonia is one of the most common serious medical complications that occurs after stroke,[1] affecting up to one third of patients with stroke.[2 3] Previous studies have indicated that post-stroke pneumonia is independently associated with poor prognoses, including higher morbidity and mortality, and decreased functional outcomes.[1 4-6] Post-stroke pneumonia is also a considerable financial burden to health-care systems.[7] Thus, developing strategies to prevent post-stroke pneumonia is an important clinical issue.

As modulators of the γ-amino butyric acid type A receptor ($GABA_A$), benzodiazepines (BZDs) are widely used for treating a variety of conditions, such as insomnia, anxiety, muscle spasm, and epilepsy.[8] Previous studies have postulated that BZDs may increase the risk of pneumonia, suggesting the cause may be related to nocturnal and daytime sedation, an increased risk of aspiration, and the possible depression of immune cells.[8-12] However, the link between BZD use and increased risk of pneumonia has been disputed by other studies,[13-17] and thus the association between these factors remains unclear.

A considerable proportion of stroke survivors are prescribed BZDs, owing to the high prevalence of post-stroke psychological problems, such as insomnia, depression, and anxiety.[16 18 19] Although post-stroke pneumonia is a serious medical complication that can lead to a poor prognosis, to our knowledge, only one prior study has addressed the association between BZD use and the risk of pneumonia development in patients post-stroke; moreover, that study utilized a short follow-up period.[16] Indeed, investigations over long-term follow-up periods in stroke survivors are still lacking. Therefore, we conducted a population-based retrospective cohort study to evaluate the association between BZD use and the risk of pneumonia in a large sample of stroke survivors over a long study period.

Methods

Data sources

We conducted a population-based retrospective cohort study by analyzing claims data obtained from Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program of Taiwan, which was launched in March 1995 and is administered by the government, is a mandatory single-payer national health insurance system that covers more than 99% of Taiwan's residents and has contracts with 97% of the hospitals and clinics in Taiwan. Data in the current study were obtained from the Longitudinal Heath Insurance Database 2000 (LHID2000), a subset of the NHIRD that contains a representative database of one million people from NHI beneficiaries registered in Taiwan in the year 2000. For research purposes, the LHID2000 was systemically and randomly sampled by the National Health Research Institute from the Taiwanese population. The database included medical claims of all inpatient, outpatient, emergency department, and home care services. Before releasing the database, information related to personal identification was encrypted to protect patient privacy and data security.[20,21] National Health Research Institute approval was obtained prior to using the LHID2000 in this study. Diagnostic disease codes were derived using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This coding is considered highly reliable in the NHIRD, as insurance claims have been investigated by medical reimbursement specialists and the coding system has undergone peer review.[22] The study protocol we applied was approved by the Institutional Review Board of Tzu Chi Medical Center. The requirement for patient consent was waived owing to the retrospective nature of this study using de-identified secondary data.

Study population

The same database used in our previous study was employed here.[21] The database is comprised of adult patients (aged ≥20 years) with new-onset stroke occurring between 2000

and 2012; patients were identified by a primary discharge diagnosis of stroke (ICD-9-CM codes 430–437). The "index date" was defined as the date of the new-onset stroke diagnosis, while "index hospitalization" was defined as concurrent hospitalization for stroke. Exclusion criteria for this study were as follows: 1) history of stroke before the 2000–2012 study period; 2) history of pneumonia 1 year preceding the index date; 3) concurrent diagnosis of pneumonia during the index hospitalization; and/or 4) death during the index hospitalization.

Exposure to benzodiazepines

In Taiwan, BZDs are controlled by the Bureau of Controlled Drugs, and patients can only obtain such drugs through a doctor's prescription. We identified BZD prescriptions written after the index hospitalization using the prescription database in the LHID. The study population was then divided into BZD and non-BZD cohorts. The BZD cohort included patients who had used any BZDs after stroke, while the non-BZD cohort was comprised of patients who were not prescribed BZDs post-stroke. To evaluate the effects of different BZD doses, we divided the BZD cohort into three subgroups using defined daily dose (DDD) methodology—a World Health Organization-recommended unit of measure employed to evaluate the prescribed amount of a drug for its main indication in an adult. Note that DDD methodology is widely used for the investigation of administrative pharmacy claim data.[20 22] Using this approach, we calculated the cumulative DDD (cDDD) by determining the sum of the dispensed DDD of all BZDs. This value was then employed to quantify BZD use during the study follow-up period. As such, the BZD cohort was divided into 1–90, 91–365, and >365 cDDD subgroups.

Outcome measures

The main outcome of this study was defined as the occurrence of pneumonia after index hospitalization, as identified by a discharge diagnosis of pneumonia (ICD-9-CM codes of

480–486). In order to increase the accuracy of this outcome, only pneumonia patients that required hospitalization were considered. To focus on the long-term prognosis, cases of pneumonia that were diagnosed during index hospitalization for stroke were excluded. The identification of patients with pneumonia using ICD-9-CM coding in inpatient service has been previously validated and shows high accuracy.[23] All subjects were followed-up on, from the index date until the first occurrence of pneumonia, death, or until December 31, 2013. Death was defined as a patient withdrawn from the NHI program,[24] as previous studies have indicated that this is an accurate and reliable proxy for date of death.[25 26] Analyses stratified by age and sex were also performed.

Covariates and propensity score matching

Baseline characteristics, such as demographic data, socioeconomic status, comorbidities, and clinical conditions, were obtained using reimbursement claims data and ICD-9-CM and procedure codes. A preexisting comorbidity was defined as a disease diagnosed at least one time during inpatient service or two times during outpatient visits within the year prior to the index date. Charlson comorbidity index scores were calculated according to information related to preexisting comorbidities.[27] Baseline medication use was defined as any medication taken for at least 30 days over the course of the year preceding the index date. Information related to stroke severity proxies was obtained based on the indicated clinical condition during the index hospitalization. Such information included diagnosis codes for hemiplegia and aphasia, operation/procedural codes for head surgery, mechanical ventilation, and utilization of the intensive care unit, as mentioned in our previous studies.[21 28] In addition, estimated National Institutes of Health Stroke Scale (NIHSS) scores were calculated to represent the severity of neurologic deficits, converting scores from a claims-based stroke severity index (SSI)—a measure specifically developed for use with Taiwan's NHIRD claims-based data—with a formula developed by Hsieh et al. (estimated NIHSS = 1.1722 × SSI −

0.7533).[29 30] The SSI has been validated in previous studies and is highly correlated with the NIHSS and consequent functional outcomes after stroke.[30-32]

Socioeconomic status was determined according to patient income and dwelling urbanization levels. Income, which was accessed based on NHI premiums, was classified into four levels (New Taiwan dollars ≥40,000, 20,000–39,999, 1–19,999, and financially dependent). Urbanization was classified into five levels, with level 1 corresponding to the most urbanized areas.[33] Detailed descriptions of income and urbanization levels have been described in our previous studies.[21 28]

In order to decrease the selection bias between groups, propensity score matching was performed to balance patient baseline characteristics, including age, sex, income level, urbanization level, comorbidities, stroke severity proxies, and medication use (Table 1). A logistic regression model was used to calculate a propensity score, which estimated the probability of BZD use based on all baseline covariates for each BZD user and non-user. Using the method of nearest-neighbor matching without replacement (with a caliper width equal to 0.2 standard deviations of the propensity score logit), we matched each BZD user with a non-BZD user.[21 34 35]

Statistical analysis

Continuous variables between the BZD and non-BZD cohort were compared using independent *t*-tests, while categorical variables were compared using chi-squared tests. The Kaplan-Meier method was performed to estimate the risk of developing pneumonia and the log-rank test was used to compare differences between cumulative incidence curves. Univariate and multivariate Cox proportional hazards regression models were used to compute the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for developing pneumonia after stroke; all baseline characteristics listed in Table 1 were adjusted for when conducting the multivariate Cox proportional hazards regression models. To

eliminate possible bias caused by competing mortality, modified Cox proportional hazards regression models were used with adjustment for competing risk events.[24 36] Differences were considered statistically significant at a two-sided probability value of <0.05. All statistical analyses were performed using Stata version 13 (Stata Corporation, College Station, TX, USA).

Results

Demographic characteristics

After propensity score matching according to the baseline characteristics listed in Table 1, a total of 7602 patients with newly onset stroke were included in our study. Among these patients, 3801 received BZDs and were classified into the BZD cohort, while 3801 did not receive BZDs and were classified into the non-BZD cohort. Although most baseline characteristics were well-balanced after propensity score matching, significant differences were found regarding the baseline prevalence of sleep disorders and the proportion of patients using anti-hypertensive agents and anxiolytics; however, the actual between-group differences were minor (Table 1).

Risk of post-stroke pneumonia according to BZD use

During a mean follow-up of 4.4 years, 1218 patients in the BZD cohort (63.9/1000 person-years), compared to 526 patients in the non-BZD cohort (35.9/1000 person-years), developed pneumonia post-stroke. A Kaplan-Meier analysis revealed a significantly higher cumulative incidence of pneumonia in the BZD than in the non-BZD cohort (log-rank test, $p < 0.0001$) (Figure 1). Cox proportional hazards regression models revealed that BZD use after stroke was associated with an increased risk of pneumonia in both the univariate (crude HR = 2.15, 95% CI = 1.94–2.38, $p < 0.001$) and multivariate models (adjusted HR [aHR] = 2.33, 95% CI = 2.09–2.59, $p < 0.001$) (Table 2).

Analyses according to different cumulative BZD doses

Patients in all three cDDD subgroups had a higher risk of developing post-stroke pneumonia than did the non-BZD cohort. The aHRs for the 1–90, 91–365, and >365 cDDD subgroups were 2.26 (95% CI = 2.01–2.53; $p < 0.001$), 2.47 (95% CI = 2.12–2.87; $p < 0.001$), and 2.52 (95% CI = 2.13–2.99; $p < 0.001$), respectively (Table 3).

Analyses after stratification for age and sex

The association between BZD use and the risk of post-stroke pneumonia development was further analyzed after stratification for age and sex (Table 4). Using this approach, we found a significantly greater risk of pneumonia in BZD users than in non-users in both age subgroups (<65 years old: aHR = 2.99, 95% CI = 2.33–3.84, $p < 0.001$; ≥65 years old: aHR = 2.16, 95% CI = 1.92–2.43, $p < 0.001$). Additionally, BZD users had an increased risk of pneumonia in both male (aHR = 2.46, 95% CI = 2.15–2.82, $p < 0.001$) and female (aHR = 2.09, 95% CI = 1.74–2.50, $p < 0.001$) subgroups (Table 4). Together, these results reveal that BZD use after stroke was associated with an increased risk of pneumonia regardless of age and sex.

Discussion

This population-based propensity-matched retrospective cohort study investigated the association between BZD use and the risk of post-stroke pneumonia. We observed that patients prescribed BZDs post-stroke had a risk of developing pneumonia that was 2.33 times higher than that for patients who had not been prescribed BZDs. To the best of our knowledge, this is the first large-scale study to demonstrate an association between BZD use and pneumonia risk in patients post-stroke over a long-term follow-up period.

Our results are consistent with those previously reported by studies that focused on the general population.[8-10] For example, previous observational studies found a 54 to 176% increase in the risk of pneumonia development in BZD users when compared to non-BZD users (relative risk or odds ratio: 1.54,[8] 1.86,[9] and 2.76 [10]). However, other observational studies have reported conflicting results, showing negative or nonsignificant relationships between BZD use and the risk of pneumonia.[13 15-17] For instance, a previous case-control study on participants aged ≥65 years old did not find a significant association between BZD use and pneumonia risk; however, only 87 BZD users were found among all of the pneumonia cases included in that study.[13] Another cross-sectional study using 30-, 60-, and 90-day windows revealed protective effects of BZDs on the risk of pneumonia, but was conducted over a relatively short study period and focused on the general population.[17]

To our knowledge, the only previous study to focus on the association between BZDs and pneumonia in stroke patients did not reveal a significant association between BZD use and the risk of pneumonia post-stroke; however, in that study, the follow-up period for identifying pneumonia was only 90 days post-stroke.[16] In contrast, the current study, which specifically focused on patients with stroke and included a large sample size and long-term follow-up period (mean follow-up time, 4.4 years), revealed a significantly increased risk of pneumonia in stroke survivors using BZDs (aHR = 2.33), even after carefully controlling for socioeconomic status, important comorbidities, stroke severity proxies, and concomitant

medications. In addition, the subgroup analyses, which were performed according to cumulative BZD doses and stratified for age and sex, also revealed a similar pattern of results, further strengthening our findings. As pneumonia is one of the most common serious medical complications following stroke and can cause not only poor functional outcomes but also high mortality and financial burdens, we believe that our study addresses a knowledge gap regarding the clinical management of patients after stroke.

Although the exact biological mechanisms underlying the influence of BZDs on pneumonia remain unclear, some hypotheses have been reported. One previous animal study suggested that BZDs may negatively influence immune function via the activation of $GABA_A$ receptors on immune cells, thus interfering with macrophages/monocytes and impairing cytokine release, phagocytosis, and bacterial killing capabilities.[11] In addition, BZDs may increase the risk of aspiration by decreasing lower esophageal sphincter pressure, inducing the relaxation of muscles in the upper respiratory tract, and depressing the swallowing reflex, ultimately leading to pharyngeal dysfunction.[10 12 37] Further research is necessary to explore these postulated mechanisms.

The strengths of the present study include its large sample size, use of a nationwide population database, and the provision of sufficient power to evaluate the effect of BZDs on the risk of pneumonia development after stroke over a long-term follow-up period. The study design also provided better evidence in terms of epidemiology than previous studies that used case-control or cross-sectional designs. Moreover, performing propensity score matching before our analyses and then using multivariate Cox proportional hazard regression models with adjustment for competing mortality allowed us to rule out several important sources of bias and ensured that confounding factors were carefully controlled.

The following limitations of the present study should also be acknowledged. First, the claim-based database did not allow for the retrieval of certain clinical information (e.g., patient lifestyle and physical, psychiatric, or laboratory examination data). Although our study

design ensured the control of several variables, unknown or unmeasured confounders could still exist. Second, the accuracy of the diagnostic coding could not be directly confirmed due to the anonymity policy enforced in the NHIRD. However, only patients who were hospitalized under a primary diagnosis of stroke were included in our study population. The identification of stroke and pneumonia using ICD-9-CM coding in inpatient services has been previously validated and shows high accuracy.[23 38 39] Additionally, the claims were routinely and randomly reviewed by the National Health Insurance Bureau to confirm the diagnostic accuracy. Given that hospitals and doctors in Taiwan are heavily fined in instances of misdiagnosis and coding errors, we feel confident in the validity of the criteria used for the inclusion of stroke and pneumonia cases in this study.

Conclusions

In summary, this population-based propensity-matched retrospective cohort study indicated an association between BZD use and an increased risk of pneumonia in patients following stroke. However, further large-scale prospective studies are needed to determine possible cause-effect relationships.

Contributors: Study conception and design: Shu-Man Lin, Huei-Kai Huang, and Ching-Hui Loh; acquisition of data: Shih-Hsien Yang and Huei-Kai Huang; analysis and interpretation of data: Shu-Man Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh; drafting of manuscript: Shu-Man Lin and Huei-Kai Huang; critical revision: Shu-Man Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh.

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Figure legends

Figure 1. Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

Table 1. Baseline characteristics of patients post-stroke in the BZD and non-BZD cohorts after propensity score matching

	BZD use				p value
	Yes (n = 3801)		No (n = 3801)		
	n	%	n	%	
Age (years)	66.2 ± 15.1		66.4 ± 14.7		0.605
Sex					0.102
Male	2510	66.0	2442	64.2	
Female	1291	34.0	1359	35.8	
Income level (NTD)					0.486
Financially dependent	1165	30.6	1146	30.1	
1–19,999	1794	47.2	1845	48.5	
20,000–39,999	520	13.7	519	13.7	
≥40,000	322	8.5	291	7.7	
Urbanization level					0.913
1 (Most urbanized)	999	26.3	990	26.0	
2	1006	26.5	1022	26.9	
3	777	20.4	748	19.7	
4	576	15.2	592	15.6	
5 (Least urbanized)	443	11.7	449	11.8	
Comorbidities					
Charlson comorbidity index	2.27 ± 1.52		2.27 ± 1.64		0.948
Hypertension	2642	69.5	2691	70.8	0.219
Diabetes mellitus	1296	34.1	1271	33.4	0.544
COPD	233	6.1	273	7.2	0.066
Asthma	110	2.9	114	3.0	0.786
Chronic kidney disease	175	4.6	198	5.2	0.222
Cirrhosis	215	5.7	212	5.6	0.881
Coronary artery disease	513	13.5	541	14.2	0.353
Congestive heart failure	196	5.2	207	5.4	0.573
Pneumoconiosis	6	0.2	7	0.2	0.781
Hyperlipidemia	1128	29.7	1085	28.5	0.278
Malignancy	201	5.3	181	4.8	0.294
Dementia	219	5.8	207	5.4	0.550
Depression	38	1.0	50	1.3	0.198
Parkinsonism	95	2.5	109	2.9	0.320

Epilepsy	23	0.6	26	0.7	0.667
Bipolar disorders	3	0.1	3	0.1	1.000
Alcohol related disorders	19	0.5	19	0.5	1.000
Substance use disorders	14	0.4	18	0.5	0.479
Schizophrenia	13	0.3	16	0.4	0.577
Anxiety	87	2.3	106	2.8	0.166
Sleep disorders	151	4.0	191	5.0	0.027
Stroke severity proxies					
Estimated NIHSS	8.0 ± 6.1		7.8 ± 5.9		0.096
ICU utilization	929	24.4	891	23.4	0.307
Mechanical ventilation	319	8.4	306	8.1	0.587
Hemiplegia	534	14.0	536	14.1	0.947
Aphasia	65	1.7	62	1.6	0.788
Neurosurgery	222	5.8	212	5.6	0.621
Use of medication					
Steroids	112	2.9	120	3.2	0.594
Anti-diabetic agents	841	22.1	833	21.9	0.825
Anti-hypertensive agents	1636	43.0	1739	45.8	0.017
Statins	335	8.8	336	8.8	0.968
Proton pump inhibitors	94	2.5	99	2.6	0.715
Anti-epileptics	65	1.7	83	2.2	0.135
Antiparkinsonian	86	2.3	91	2.4	0.704
Antipsychotics	90	2.4	84	2.2	0.645
Anxiolytics	229	6.0	297	7.8	0.002
Hypnotics and sedatives	164	4.3	184	4.8	0.272
Antidepressants	96	2.5	100	2.6	0.772

Continuous data expressed as mean ± standard deviation (SD) and categorical data expressed as number and percentage.

Abbreviations: BZD, benzodiazepine; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan dollars; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Risk of pneumonia after stroke among patients in the BZD and non-BZD cohorts

	BZD use	
	Yes	No
Patient numbers	3801	3801
Pneumonia cases	1218	526
Person-years	19064.7	14659.8
Incidence rate*	63.9	35.9
Univariate model		
Crude HR (95% CI)	2.15 (1.94–2.38)	1 (ref.)
p value	<0.001	
Multivariate model†		
Adjusted HR (95% CI)	2.33 (2.09–2.59)	1 (ref.)
p value	<0.001	

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

Table 3. Risk of pneumonia after stroke according to different cumulative BZD doses

Cumulative BZD doses	n	Pneumonia cases	Person-years	Incidence rate*	Univariate model		Multivariate model†	
					Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	3801	526	14659.8	35.9	1 (ref.)		1 (ref.)	
1–90 cDDDs	2572	816	11690.1	69.8	2.21 (1.98–2.46)	<0.001	2.26 (2.01–2.53)	<0.001
91–365 cDDDs	734	247	4040.9	61.1	2.18 (1.88–2.52)	<0.001	2.47 (2.12–2.87)	<0.001
>365 cDDDs	495	155	3333.7	46.5	1.84 (1.55–2.19)	<0.001	2.52 (2.13–2.99)	<0.001

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDDs, cumulative defined daily doses

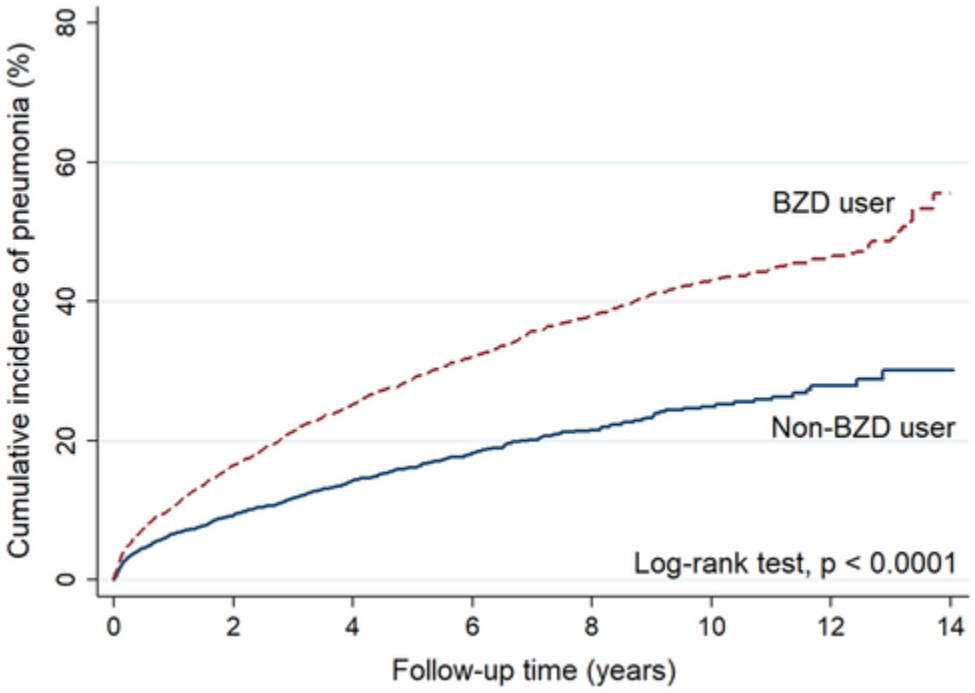
Table 4. Risk of pneumonia after stroke in the BZD and non-BZD cohorts after stratification for age and sex

	BZD use				Non-BZD use				Univariate model		Multivariate model†	
	n	Pneumonia cases	Person-years	Incidence rate*	n	Pneumonia cases	Person-years	Incidence rate*	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Age												
<65	1590	278	10122.3	27.5	1632	83	7568.4	11.0	2.87 (2.25–3.67)	<0.001	2.99 (2.33–3.84)	<0.001
≥65	2211	940	8942.4	105.1	2169	443	7091.4	62.5	2.06 (1.84–2.30)	<0.001	2.16 (1.92–2.43)	<0.001
Sex												
Male	2510	848	12580.0	67.4	2442	313	9944.7	31.5	2.46 (2.16–2.80)	<0.001	2.46 (2.15–2.82)	<0.001
Female	1291	370	6484.6	57.1	1359	213	4715.1	45.2	1.68 (1.42–1.98)	<0.001	2.09 (1.74–2.50)	<0.001

*Per 1,000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval



Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

42x29mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number in manuscript
✓ **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
✓ Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
✓ Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
✓ Study design	4	Present key elements of study design early in the paper	6-8
✓ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
✓ Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8-9 Table 1
✓ Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
✓ Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
✓ Bias	9	Describe any efforts to address potential sources of bias	8-10
✓ Study size	10	Explain how the study size was arrived at	6-7
✓ Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
✓ Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
✓ Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
✓ Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 p.11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	11
✓ Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2-4

			p.11-12
✓ Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12 Table 1
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
✓ Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
✓ Key results	18	Summarise key results with reference to study objectives	13
✓ Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
✓ Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
✓ Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
✓ Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between benzodiazepine use and pneumonia risk among patients with stroke: A population-based cohort study

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The association between benzodiazepine use and pneumonia risk among patients with stroke: A population-based cohort study

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Abstract

Objectives

To investigate the association between benzodiazepine (BZD) use and the risk of chronic-onset post-stroke pneumonia.

Design

Population-based propensity-matched retrospective cohort study.

Setting

Taiwan's National Health Insurance Research Database.

Participants

Patients newly diagnosed with stroke between 2000 and 2012 were identified and, after propensity score matching, 7516 patients were enrolled. Among these, 3758 patients received BZDs after stroke while 3758 did not.

Outcome measures

Hazard ratios (HRs) for developing pneumonia over 1 month after stroke according to BZD use were assessed using Cox proportional hazards regression models. Analyses according to cumulative defined daily doses (cDDDs) of BZDs and stratification for age and sex were also performed.

Results

During a mean follow-up time of 4.4 years, 1027 patients in the BZD cohort and 478 patients in the non-BZD cohort developed pneumonia over 1 month after stroke. Patients using BZDs after stroke had a higher pneumonia risk than did those not using BZDs (52.2 vs. 32.6 per 1000 person-years, adjusted HR [aHR] = 2.21, 95% confidence interval [CI] = 1.97–2.48, $p < 0.001$). Analyses based on cumulative BZD dose revealed that all BZD user subgroups were associated with a higher risk of pneumonia. The aHRs for patients taking 1–90, 91–365, and >365 cDDDs

of BZDs were 2.28 (95% CI = 2.01–2.58; p < 0.001), 2.09 (95% CI = 1.77–2.47; p < 0.001), and 2.08 (95% CI = 1.72–2.52; p < 0.001), respectively. The significant association between BZD use and increased pneumonia risk persisted even after stratifying subgroups by age and sex.

Conclusions

BZD use is associated with an increased risk of chronic-onset post-stroke pneumonia.

Strengths and limitations of this study

- This retrospective cohort study was performed based on a nationwide population database, which contained one million subjects randomly sampled from Taiwan's population.
- This is the first large-scale study to demonstrate an association between benzodiazepine use and pneumonia risk in stroke patients over a long-term follow-up period.
- The claim-based data did not allow for the retrieval of certain clinical information (e.g., patient lifestyle and physical, psychiatric, or laboratory examination data), and thus we could not control or adjust for these potential confounders in our analyses.

Introduction

Pneumonia is one of the most common serious medical complications that occurs after stroke,[1] affecting up to one third of patients with stroke.[2 3] Previous studies have indicated that post-stroke pneumonia is independently associated with poor prognoses, including higher morbidity and mortality, and decreased functional outcomes.[1 4-6] Post-stroke pneumonia can be divided into two types according to the time of occurrence: acute-onset refers to pneumonia developed within 1 month of the stroke event, while chronic onset was referred as pneumonia developed after 1 month of stroke.[7] Post-stroke pneumonia is also a considerable financial burden to health-care systems.[8] Thus, developing strategies to prevent post-stroke pneumonia is an important clinical issue.

As modulators of the γ-amino butyric acid type A receptor ($GABA_A$), benzodiazepines (BZDs) are widely used for treating a variety of conditions, such as insomnia, anxiety, muscle spasm, and epilepsy.[9] Previous studies have postulated that BZDs may increase the risk of pneumonia, possibly on account of nocturnal and daytime sedation, an increased risk of aspiration, and the possible depression of immune cells.[9-13] However, the link between BZD use and increased risk of pneumonia has been disputed by other studies,[14-18] and thus the association between these factors remains unclear.

A considerable proportion of stroke survivors are prescribed BZDs, owing to the high prevalence of post-stroke psychological problems, such as insomnia, depression, and anxiety.[17 19 20] Although pneumonia is a serious medical complication that can lead to a poor prognosis, to our knowledge, only one prior study has addressed the association between BZD use and the risk of pneumonia development in patients post-stroke; moreover, that study utilized a short follow-up period.[17] Indeed, investigations into chronic-onset post-stroke pneumonia over long-term follow-up periods in stroke survivors are still lacking. Therefore, we conducted a

population-based retrospective cohort study to evaluate the association between BZD use and the risk of chronic-onset post-stroke pneumonia in a large sample of stroke survivors over a long study period.

Methods

Data sources

We conducted a population-based retrospective cohort study by analyzing claims data obtained from Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program of Taiwan, which was launched in March 1995 and is administered by the government, is a mandatory single-payer national health insurance system that covers more than 99% of Taiwan's residents and has contracts with 97% of the hospitals and clinics in Taiwan. Data in the current study were obtained from the Longitudinal Heath Insurance Database 2000 (LHID2000), a subset of the NHIRD that contains a representative database of one million people from NHI beneficiaries registered in Taiwan in the year 2000. For research purposes, the LHID2000 was systemically and randomly sampled by the National Health Research Institute from the Taiwanese population. The database included medical claims of all inpatient, outpatient, emergency department, and home care services. Before releasing the database, information related to personal identification was encrypted to protect patient privacy and data security.[21 22] National Health Research Institute approval was obtained prior to using the LHID2000 in this study. Diagnostic disease codes were derived using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This coding is considered highly reliable in the NHIRD, as insurance claims have been investigated by medical reimbursement specialists and the coding system has undergone peer review.[23] The study protocol we applied was approved by the Institutional Review Board of Tzu Chi Medical Center.

The requirement for patient consent was waived owing to the retrospective nature of this study using de-identified secondary data.

Study population

The same database used in our previous study was employed here.[22] The database is comprised of adult patients (aged ≥20 years) with new-onset stroke occurring between 2000 and 2012; patients were identified by a primary discharge diagnosis of stroke (ICD-9-CM codes 430–437). The "index date" was defined as the date of the new-onset stroke diagnosis, while "index hospitalization" was defined as concurrent hospitalization for stroke. Exclusion criteria for this study were as follows: 1) history of stroke before the 2000–2012 study period; 2) history of pneumonia 1 year preceding the index date; 3) concurrent diagnosis of pneumonia during the index hospitalization; and/or 4) death during the index hospitalization.

Exposure to benzodiazepines

In Taiwan, BZDs are controlled by the Bureau of Controlled Drugs, and patients can only obtain such drugs through a doctor's prescription. We identified BZD prescriptions written after the index hospitalization using the prescription database in the LHID. The study population was then divided into BZD and non-BZD cohorts. The BZD cohort included patients who had used any BZDs after stroke during the follow-up period, while the non-BZD cohort was comprised of patients who were not prescribed BZDs post-stroke. To evaluate the effects of different BZD doses, we divided the BZD cohort into three subgroups using defined daily dose (DDD) methodology—a World Health Organization-recommended unit of measure employed to evaluate the prescribed amount of a drug for its main indication in an adult. Note that DDD methodology is widely used for the investigation of administrative pharmacy claim data.[21 23] Using this

approach, we calculated the cumulative DDD (cDDD) by determining the sum of the dispensed DDD of all BZDs. This value was then employed to quantify BZD use during the study follow-up period. As such, the BZD cohort was divided into 1–90, 91–365, and >365 cDDD subgroups.

Outcome measures and sensitivity analysis

The main outcome of this study was defined as the occurrence of chronic-onset post-stroke pneumonia after index hospitalization, as identified by a discharge diagnosis of pneumonia (ICD-9-CM codes of 480–486). In order to increase the accuracy of this outcome, only pneumonia patients that required hospitalization were considered. According to previous research, chronic-onset post-stroke pneumonia is defined as pneumonia developing over 1 month after the incidence of stroke.[7] As the present study evaluated chronic-onset post-stroke pneumonia, cases of pneumonia diagnosed within 30 days of the stroke event were excluded. The identification of patients with pneumonia using ICD-9-CM coding in inpatient service has been previously validated and shows high accuracy.[24] All subjects were followed-up on, from the index date until the first occurrence of pneumonia, death, or until December 31, 2013. Death was defined as a patient withdrawn from the NHI program,[25] as previous studies have indicated that this is an accurate and reliable proxy for date of death.[26 27] Analyses stratified by age and sex were also performed.

In addition, to examine whether a diagnosis of pneumonia rendered in an outpatient service would influence our results, we performed a sensitivity analysis. For this analysis, pneumonia events were defined as those diagnosed during the follow-up period regardless of whether the diagnosis was rendered in an inpatient or outpatient service.

Covariates and propensity score matching

Baseline characteristics, such as demographic data, socioeconomic status, comorbidities, and clinical conditions, were obtained using reimbursement claims data and ICD-9-CM and procedure codes. A preexisting comorbidity was defined as a disease diagnosed at least one time during inpatient service or two times during outpatient visits within the year prior to the index date. The Charlson comorbidity index was calculated according to information related to preexisting comorbidities.[28] Baseline medication use was defined as any medication taken for at least 30 days over the course of the year preceding the index date. Information related to stroke severity proxies was obtained based on the indicated clinical condition during the index hospitalization. Such information included diagnosis codes for hemiplegia and aphasia, operation/procedural codes for head surgery, mechanical ventilation, and utilization of the intensive care unit, as mentioned in our previous studies.[22 29] In addition, estimated National Institutes of Health Stroke Scale (NIHSS) scores were calculated to represent the severity of neurologic deficits, converting scores from a claims-based stroke severity index (SSI)—a measure specifically developed for use with Taiwan's NHIRD claims-based data—with a formula developed by Hsieh et al. (estimated NIHSS = 1.1722 × SSI − 0.7533).[30 31] The SSI has been validated in previous studies and is highly correlated with the NIHSS and consequent functional outcomes after stroke.[31-33] Additionally, some comorbidities may occur after stroke and also possibly cause a confounding effect. We therefore calculated an additional Charlson comorbidity index at the end point of follow-up, using the data on comorbidities from the year prior to the end-point date. Socioeconomic status was determined according to patient income and dwelling urbanization levels. Income, which was accessed based on NHI premiums, was classified into four levels (New Taiwan dollars ≥40,000, 20,000–39,999, 1–19,999, and financially dependent). Urbanization was classified into five levels, with level 1 corresponding to the most urbanized areas.[34] Detailed descriptions of income and urbanization levels have been

described in our previous studies.[22 29]

In order to decrease the selection bias between groups, propensity score matching was performed to balance patient baseline characteristics, including age, sex, income level, urbanization level, comorbidities, Charlson comorbidity index, stroke severity proxies, and medication use (Table 1). A logistic regression model was used to calculate a propensity score, which estimated the probability of BZD use based on all baseline covariates for each BZD user and non-user. Using the method of nearest-neighbor matching without replacement (with a caliper width equal to 0.2 standard deviations of the propensity score logit), we matched each BZD user with a non-BZD user.[22 35 36]

Statistical analysis

Continuous variables between the BZD and non-BZD cohort were compared using independent *t*-tests, while categorical variables were compared using chi-squared tests. The Kaplan-Meier method was performed to estimate the risk of developing pneumonia and the log-rank test was used to compare differences between cumulative incidence curves. Univariate and multivariate Cox proportional hazards regression models were used to compute the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for developing pneumonia after stroke; all baseline characteristics listed in Table 1 were adjusted for when conducting the multivariate Cox proportional hazards regression models. To eliminate possible bias caused by competing mortality, modified Cox proportional hazards regression models were used with adjustment for competing risk events.[25 37] Differences were considered statistically significant at a two-sided probability value of <0.05. All statistical analyses were performed using Stata version 13 (Stata Corporation, College Station, TX, USA).

Patient and public involvement

Due to the present study having used de-identified secondary data, the patients and public were not directly involved in this study and the need for consent was waived.

Results

Demographic characteristics

After propensity score matching according to the baseline characteristics listed in Table 1, a total of 7516 patients with newly onset stroke were included in our study. Among these patients, 3758 received BZDs and were classified into the BZD cohort, while 3758 did not receive BZDs and were classified into the non-BZD cohort. Although most baseline characteristics were well-balanced after propensity score matching, significant differences were found regarding the baseline prevalence of sleep disorders and the proportion of patients using anti-hypertensive agents and anxiolytics; however, the actual between-group differences were minor (Table 1).

Risk of chronic-onset post-stroke pneumonia according to BZD use

During a mean follow-up of 4.4 years, 1027 patients in the BZD cohort (52.2/1000 person-years), compared to 478 patients in the non-BZD cohort (32.6/1000 person-years), developed pneumonia. A Kaplan-Meier analysis revealed a significantly higher cumulative incidence of pneumonia in the BZD than in the non-BZD cohort (log-rank test, $p < 0.0001$) (Figure 1). Cox proportional hazards regression models revealed that BZD use after stroke was associated with an increased risk of pneumonia in both the univariate (crude HR = 1.95, 95% CI = 1.75–2.17, $p < 0.001$) and multivariate models (adjusted HR [aHR] = 2.21, 95% CI = 1.97–2.48, $p < 0.001$) (Table 2).

Analyses according to different cumulative BZD doses

Patients in all three cDDD subgroups had a higher risk of developing pneumonia than did the non-BZD cohort. The aHRs for the 1–90, 91–365, and >365 cDDD subgroups were 2.28 (95% CI = 2.01–2.58; $p < 0.001$), 2.09 (95% CI = 1.77–2.47; $p < 0.001$), and 2.08 (95% CI =

1.72–2.52; $p < 0.001$), respectively (Table 3).

Analyses after stratification for age and sex

The association between BZD use and the risk of pneumonia development in stroke patients was further analyzed after stratification for age and sex (Table 4). Using this approach, we found a significantly greater risk of pneumonia in BZD users than in non-users in both age subgroups (<65 years old: aHR = 2.42, 95% CI = 1.84–3.17, $p < 0.001$; ≥65 years old: aHR = 2.11, 95% CI = 1.86–2.40, $p < 0.001$). Additionally, BZD users had an increased risk of pneumonia in both male (aHR = 2.46, 95% CI = 2.13–2.84, $p < 0.001$) and female (aHR = 1.83, 95% CI = 1.50–2.22, $p < 0.001$) subgroups (Table 4). Together, these results reveal that BZD use after stroke was associated with an increased risk of pneumonia regardless of age and sex.

Results of sensitivity analysis

In the sensitivity analysis, which considered the pneumonia event regardless of diagnosis in inpatient or outpatient service, BZD use was independently associated with increased risk of developing pneumonia (adjusted HR = 1.94, 95% CI = 1.77- 2.14, $p < 0.001$). The results for different cumulative doses of BZDs also revealed a pattern to our primary analyses. The detailed statistical values are shown in the Supplementary materials (Supplementary Table S1).

Discussion

This population-based propensity-matched retrospective cohort study investigated the association between BZD use and the risk of chronic-onset post-stroke pneumonia. We observed that patients prescribed BZDs post-stroke had a risk of developing pneumonia that was 2.21 times higher than that for patients who had not been prescribed BZDs. To the best of our knowledge, this is the first large-scale study to demonstrate an association between BZD use and the risk of chronic-onset post-stroke pneumonia over a long-term follow-up period.

Our results are consistent with those previously reported by studies that focused on the general population.[9-11] For example, previous observational studies found a 54 to 176% increase in the risk of pneumonia development in BZD users when compared to non-BZD users (relative risk or odds ratio: 1.54,[9] 1.86,[10] and 2.76 [11]). However, other observational studies have reported conflicting results, showing negative or nonsignificant relationships between BZD use and the risk of pneumonia.[14 16-18] For instance, a previous case-control study on participants aged ≥65 years old did not find a significant association between BZD use and pneumonia risk; however, only 87 BZD users were found among all of the pneumonia cases included in that study.[14] Another cross-sectional study using 30-, 60-, and 90-day windows revealed protective effects of BZDs on the risk of pneumonia, but was conducted over a relatively short study period and focused on the general population.[18]

Pneumonia is a significant complication in stroke patients owing to the increased risk of apparent aspiration and dysphagia-associated microaspiration, as well as stroke-induced immunodepression.[6 7 38] Acute-onset post-stroke pneumonia, which develops within 1 month of the stroke event, is mainly associated with apparent aspiration and stroke-induced immunodepression.[6 7] However, although apparent aspiration and immunodepression gradually attenuate following stroke recovery, the silent aspiration or microaspiration into the lower

airways may still occur and cause chronic-onset post-stroke pneumonia.[7 39] BZDs are commonly used in stroke patients on account of the high prevalence of psychological problems in stroke patients;[17 19 20] previous studies have indicated that BZDs may be associated with the increased risk of aspiration and depression of immune cells.[9-13] To the best of our knowledge, the only previous study to focus on the association between BZDs and pneumonia in stroke patients did not reveal a significant association between BZD use and the risk of pneumonia post-stroke; however, in that study, the follow-up period for identifying pneumonia was only 90 days post-stroke.[17] In contrast, the current study, which specifically focused on the chronic phase of post-stroke to evaluate pneumonia developed over 1 month after the stroke,[7] included a large sample size and long-term follow-up period (mean follow-up time, 4.4 years). The present study revealed a significantly increased risk of chronic-onset pneumonia in stroke survivors using BZDs (aHR = 2.21), even after carefully controlling for socioeconomic status, important comorbidities, stroke severity proxies, and concomitant medications. In addition, the subgroup analyses, which were performed according to cumulative BZD doses and stratified for age and sex, also revealed a similar pattern of results, further strengthening our findings. As pneumonia is one of the most common serious medical complications following stroke and can cause not only poor functional outcomes but also high mortality and financial burdens, we believe that our study addresses a knowledge gap regarding the clinical management of patients after stroke.

Although the exact biological mechanisms underlying the influence of BZDs on pneumonia remain unclear, some hypotheses have been reported. One previous animal study suggested that BZDs may negatively influence immune function via the activation of $GABA_A$ receptors on immune cells, thus interfering with macrophages/monocytes and impairing cytokine release, phagocytosis, and bacterial killing capabilities.[12] In addition, BZDs may increase the risk of aspiration by decreasing lower esophageal sphincter pressure, inducing the relaxation of muscles

in the upper respiratory tract, and depressing the swallowing reflex, ultimately leading to pharyngeal dysfunction.[11 13 40] Further research is necessary to explore these postulated mechanisms.

The strengths of the present study include its large sample size, use of a nationwide population database, and the provision of sufficient power to evaluate the effect of BZDs on the risk of pneumonia development after stroke over a long-term follow-up period. The study design also provided better evidence in terms of epidemiology than previous studies that used case-control or cross-sectional designs. Moreover, performing propensity score matching before our analyses and then using multivariate Cox proportional hazard regression models with adjustment for competing mortality allowed us to rule out several important sources of bias and ensured that confounding factors were carefully controlled.

The following limitations of the present study should also be acknowledged. First, the claim-based database did not allow for the retrieval of certain clinical information (e.g., patient lifestyle and physical, psychiatric, or laboratory examination data). Although our study design ensured the control of several variables, unknown or unmeasured confounders could still exist. Second, by using de-identified claims, we could not obtain the patient details to analyze the medical history and identify exact mechanism of pneumonia; thus, we could not determine whether the pneumonia was caused by aspiration or not. Third, our analyses performed according to different cumulative BZD doses did not reveal an obvious dose-effect relationship. It is difficult to completely avoid an indication bias in observational studies that evaluate the effect of medication or intervention. Hence, the existence of unidentified residual confounders cannot be completely ruled out from the present study. Thus, further prospective clinical trials are necessary to determine the cause-and-effect relationship between post-stroke BZD use and the pneumonia risk. Finally, the accuracy of the diagnostic coding could not be directly confirmed due to the

anonymity policy enforced in the NHIRD. However, only patients who were hospitalized under a primary diagnosis of stroke were included in our study population. The identification of stroke and pneumonia using ICD-9-CM coding in inpatient services has been previously validated and shows high accuracy.[24 41 42] Additionally, the claims were routinely and randomly reviewed by the National Health Insurance Bureau to confirm the diagnostic accuracy. Given that hospitals and doctors in Taiwan are heavily fined in instances of misdiagnosis and coding errors, we feel confident in the validity of the criteria used for the inclusion of stroke and pneumonia cases in this study.

Conclusions

In summary, this population-based propensity-matched retrospective cohort study indicated an association between BZD use and an increased risk of chronic-onset post-stroke pneumonia. However, further large-scale prospective studies are needed to determine possible cause-effect relationships.

Contributors: Study conception and design: Shu-Man Lin, Huei-Kai Huang, and Ching-Hui Loh; acquisition of data: Shih-Hsien Yang and Huei-Kai Huang; analysis and interpretation of data: Shu-Man Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh; drafting of manuscript: Shu-Man Lin and Huei-Kai Huang; critical revision: Shu-Man Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh.

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Figure legends

Figure 1. Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

Table 1. Baseline characteristics of patients post-stroke in the BZD and non-BZD cohorts after propensity score matching

	BZD use				p value
	Yes (n = 3,758)		No (n = 3,758)		
	n	%	n	%	
Age (years)	66.2 ± 14.9		66.3 ± 14.7		0.941
Sex					0.267
Male	2,455	65.3	2,409	64.1	
Female	1,303	34.7	1,349	35.9	
Income level (NTD)					0.816
Financially dependent	1,123	29.9	1,125	29.9	
1–19,999	1,801	47.9	1,826	48.6	
20,000–39,999	522	13.9	516	13.7	
≥40,000	312	8.3	291	7.7	
Urbanization level					0.732
1 (Most urbanized)	974	25.9	985	26.2	
2	993	26.4	1,010	26.9	
3	791	21.0	744	19.8	
4	579	15.4	580	15.4	
5 (Least urbanized)	421	11.2	439	11.7	
Comorbidities					
Charlson comorbidity index	2.26 ± 1.50		2.27 ± 1.63		0.837
Hypertension	2,666	70.9	2,666	70.9	1.000
Diabetes mellitus	1,263	33.6	1,256	33.4	0.864
COPD	247	6.6	265	7.1	0.410
Asthma	114	3.0	112	3.0	0.893
Chronic kidney disease	180	4.8	198	5.3	0.342
Cirrhosis	200	5.3	207	5.5	0.721
Coronary artery disease	491	13.1	528	14.1	0.213
Congestive heart failure	192	5.1	202	5.4	0.605
Pneumoconiosis	6	0.2	7	0.2	0.781
Hyperlipidemia	1,096	29.2	1,080	28.7	0.684
Malignancy	188	5.0	176	4.7	0.519

Dementia	207	5.5	208	5.5	0.960
Depression	34	0.9	50	1.3	0.079
Parkinsonism	107	2.8	106	2.8	0.945
Epilepsy	24	0.6	26	0.7	0.777
Bipolar disorders	3	0.1	3	0.1	1.000
Alcohol related disorders	14	0.4	19	0.5	0.383
Substance use disorders	18	0.5	18	0.5	1.000
Schizophrenia	18	0.5	16	0.4	0.731
Anxiety	90	2.4	104	2.8	0.309
Sleep disorders	170	4.5	186	4.9	0.385
Charlson comorbidity index at the end point of follow-up	2.03 ± 1.79		2.13 ± 2.06		0.022
Stroke severity proxies					
Estimated NIHSS	8.0 ± 6.0		7.7 ± 5.8		0.061
ICU utilization	937	24.9	871	23.2	0.075
Mechanical ventilation	308	8.2	299	8.0	0.703
Hemiplegia	562	15.0	530	14.1	0.295
Aphasia	69	1.8	63	1.7	0.598
Neurosurgery	202	5.4	210	5.6	0.685
Use of medication					
Steroids	109	2.9	116	3.1	0.636
Anti-diabetic agents	795	21.2	821	21.8	0.465
Anti-hypertensive agents	1,676	44.6	1,715	45.6	0.366
Statins	319	8.5	332	8.8	0.594
Proton pump inhibitors	89	2.4	97	2.6	0.553
Anti-epileptics	70	1.9	82	2.2	0.325
Antiparkinsonian	92	2.4	90	2.4	0.881
Antipsychotics	76	2.0	85	2.3	0.473
Anxiolytics	246	6.5	286	7.6	0.072
Hypnotics and sedatives	156	4.2	180	4.8	0.180
Antidepressants	79	2.1	97	2.6	0.170

Continuous data expressed as mean ± standard deviation (SD) and categorical data expressed as number and percentage.

Abbreviations: BZD, benzodiazepine; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan dollars; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Risk of pneumonia after stroke among patients in the BZD and non-BZD cohorts

	BZD use	
	Yes	No
Patient numbers	3758	3758
Pneumonia cases	1027	478
Person-years	19680.1	14663.8
Incidence rate*	52.2	32.6
Univariate model		
Crude HR (95% CI)	1.95 (1.75–2.17)	1 (ref.)
p value	<0.001	
Multivariate model†		
Adjusted HR (95% CI)	2.21 (1.97–2.48)	1 (ref.)
p value	<0.001	

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

Table 3. Risk of pneumonia after stroke according to different cumulative BZD doses

Cumulative BZD doses	n	Pneumonia cases	Person-years	Incidence rate*	Univariate model		Multivariate model†	
					Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	3758	478	14663.8	32.6	1 (ref.)		1 (ref.)	
1–90 cDDDs	2507	702	11760.2	59.7	2.10 (1.87–2.36)	<0.001	2.28 (2.01–2.58)	<0.001
91–365 cDDDs	728	198	4216.6	47.0	1.84 (1.56–2.16)	<0.001	2.09 (1.77–2.47)	<0.001
>365 cDDDs	523	127	3703.4	34.3	1.47 (1.21–1.77)	<0.001	2.08 (1.72–2.52)	<0.001

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDDs, cumulative defined daily doses

Table 4. Risk of pneumonia after stroke in the BZD and non-BZD cohorts after stratification for age and sex

	BZD use				Non-BZD use				Univariate model		Multivariate model†	
	n	Pneumonia cases	Person-years	Incidence rate*	n	Pneumonia cases	Person-years	Incidence rate*	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Age												
<65	1599	221	10438.4	21.2	1626	77	7568.1	10.2	2.32 (1.79–3.00)	<0.001	2.42 (1.84–3.17)	<0.001
≥65	2159	806	9241.7	87.2	2132	401	7095.7	56.5	1.94 (1.72–2.18)	<0.001	2.11 (1.86–2.40)	<0.001
Sex												
Male	2455	721	12709.5	56.7	2409	278	9945.3	28.0	2.35 (2.04–2.69)	<0.001	2.46 (2.13–2.84)	<0.001
Female	1303	306	6970.6	43.9	1349	200	4718.5	42.4	1.39 (1.16–1.66)	<0.001	1.83 (1.50–2.22)	<0.001

*Per 1,000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

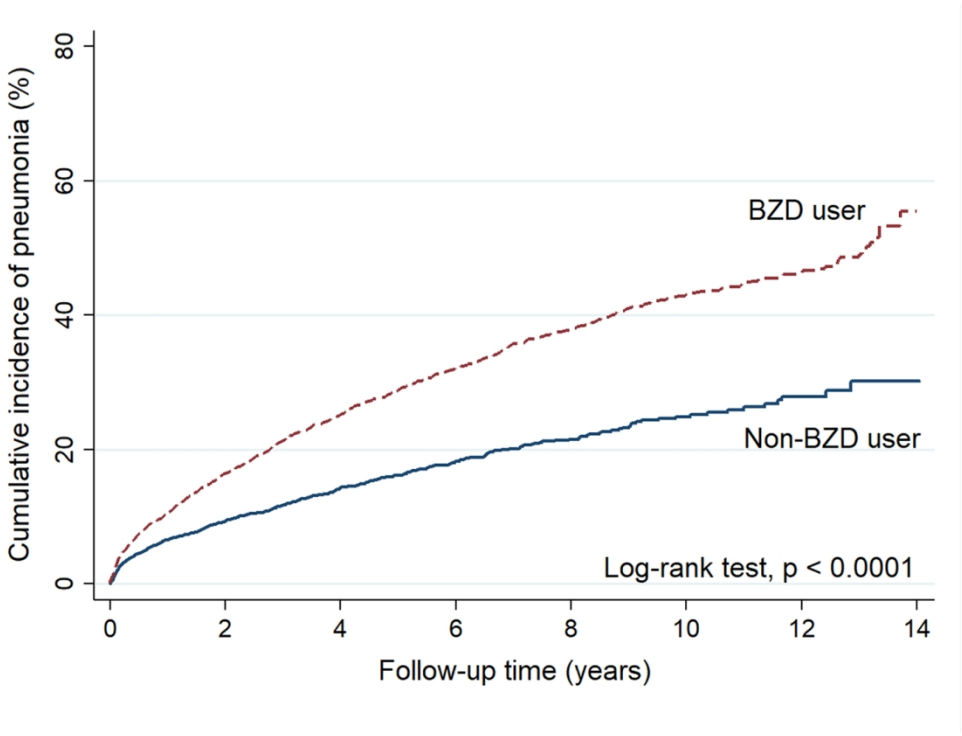

Figure 1. Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

127x92mm (300 x 300 DPI)

Supplementary Materials

Table S1. Sensitivity analysis of risk of contracting pneumonia after stroke according to BZD-use status

Cumulative BZD doses	Univariate model		Multivariate model†	
	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	1 (ref.)		1 (ref.)	
All BZD user	1.75 (1.60–1.91)	<0.001	1.94 (1.77–2.14)	<0.001
1–90 cDDDs	1.83 (1.66–2.02)	<0.001	1.96 (1.77–2.18)	<0.001
91–365 cDDDs	1.72 (1.50–1.98)	<0.001	1.89 (1.64–2.18)	<0.001
>365 cDDDs	1.45 (1.24–1.70)	<0.001	1.92 (1.63–2.25)	<0.001

For the sensitivity analysis, pneumonia events were defined as those diagnosed during the follow-up period regardless of whether the diagnosis was rendered in an inpatient or outpatient service.

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDDs, cumulative defined daily doses

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number in manuscript
✓ **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
✓ Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
✓ Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
✓ Study design	4	Present key elements of study design early in the paper	6-8
✓ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
✓ Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8-9 Table 1
✓ Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
✓ Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
✓ Bias	9	Describe any efforts to address potential sources of bias	8-10
✓ Study size	10	Explain how the study size was arrived at	6-7
✓ Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
✓ Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	8
Results			
✓ Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
✓ Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 p.11
		(b) Indicate number of participants with missing data for each	N/A

		variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	11
✓ Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2-4 p.11-12
✓ Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12 Table 1
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
✓ Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
✓ Key results	18	Summarise key results with reference to study objectives	13
✓ Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
✓ Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
✓ Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
✓ Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between benzodiazepine use and risks of chronic-onset post-stroke pneumonia: A population-based cohort study

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The association between benzodiazepine use and risks of chronic-onset post-stroke pneumonia: A population-based cohort study

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Word Count: 3283

Abstract

Objectives

To investigate the association between benzodiazepine (BZD) use and the risk of chronic-onset post-stroke pneumonia.

Design

Population-based propensity-matched retrospective cohort study.

Setting

Taiwan's National Health Insurance Research Database.

Participants

Patients newly diagnosed with stroke between 2000 and 2012 were identified and, after propensity score matching, 7516 patients were enrolled. Among these, 3758 patients received BZDs after stroke while 3758 did not.

Outcome measures

Hazard ratios (HRs) for developing pneumonia over 1 month after stroke according to BZD use were assessed using Cox proportional hazards regression models. Analyses according to cumulative defined daily doses (cDDDs) of BZDs and stratification for age and sex were also performed.

Results

During a mean follow-up time of 4.4 years, 1027 patients in the BZD cohort and 478 patients in the non-BZD cohort developed pneumonia over 1 month after stroke. Patients using BZDs after stroke had a higher pneumonia risk than did those not using BZDs (52.2 vs. 32.6 per 1000 person-years, adjusted HR [aHR] = 2.21, 95% confidence interval [CI] = 1.97–2.48, $p < 0.001$). Analyses based on cumulative BZD dose revealed that all BZD user subgroups were associated with a higher risk of pneumonia. The aHRs for patients taking 1–90, 91–365, and >365 cDDDs of BZDs were 2.28 (95% CI = 2.01–2.58; $p < 0.001$), 2.09 (95% CI = 1.77–2.47; $p < 0.001$), and 2.08 (95% CI = 1.72–2.52; $p < 0.001$), respectively. The significant

association between BZD use and increased pneumonia risk persisted even after stratifying subgroups by age and sex.

Conclusions

BZD use is associated with an increased risk of chronic-onset post-stroke pneumonia.

Strengths and limitations of this study

- This retrospective cohort study was performed based on a nationwide population database, which contained one million subjects randomly sampled from Taiwan's population.
- This is the first large-scale study to demonstrate an association between benzodiazepine use and pneumonia risk in stroke patients over a long-term follow-up period.
- The claim-based data did not allow for the retrieval of certain clinical information (e.g., patient lifestyle and physical, psychiatric, or laboratory examination data), and thus we could not control or adjust for these potential confounders in our analyses.

Introduction

Pneumonia is one of the most common serious medical complications that occurs after stroke,[1] affecting up to one third of patients with stroke.[2 3] Previous studies have indicated that post-stroke pneumonia is independently associated with poor prognoses, including higher morbidity and mortality, and decreased functional outcomes.[1 4-6] Post-stroke pneumonia can be divided into two types according to the time of occurrence: acute-onset refers to pneumonia developed within 1 month of the stroke event, while chronic onset was referred as pneumonia developed after 1 month of stroke.[7] Post-stroke pneumonia is also a considerable financial burden to health-care systems.[8] Thus, developing strategies to prevent post-stroke pneumonia is an important clinical issue.

As modulators of the γ-amino butyric acid type A receptor ($GABA_A$), benzodiazepines (BZDs) are widely used for treating a variety of conditions, such as insomnia, anxiety, muscle spasm, and epilepsy.[9] Previous studies have postulated that BZDs may increase the risk of pneumonia, possibly on account of nocturnal and daytime sedation, an increased risk of aspiration, and the possible depression of immune cells.[9-13] However, the link between BZD use and increased risk of pneumonia has been disputed by other studies,[14-18] and thus the association between these factors remains unclear.

A considerable proportion of stroke survivors are prescribed BZDs, owing to the high prevalence of post-stroke psychological problems, such as insomnia, depression, and anxiety.[17 19 20] Although pneumonia is a serious medical complication that can lead to a poor prognosis, to our knowledge, only one prior study has addressed the association between BZD use and the risk of pneumonia development in patients post-stroke; moreover, that study utilized a short follow-up period.[17] Indeed, investigations into chronic-onset post-stroke pneumonia over long-term follow-up periods in stroke survivors are still lacking. Therefore, we conducted a population-based retrospective cohort study to evaluate the association between BZD use and the risk of chronic-onset post-stroke pneumonia in a large sample of

stroke survivors over a long study period.

Methods

Data sources

We conducted a population-based retrospective cohort study by analyzing claims data obtained from Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program of Taiwan, which was launched in March 1995 and is administered by the government, is a mandatory single-payer national health insurance system that covers more than 99% of Taiwan's residents and has contracts with 97% of the hospitals and clinics in Taiwan. Data in the current study were obtained from the Longitudinal Heath Insurance Database 2000 (LHID2000), a subset of the NHIRD that contains a representative database of one million people from NHI beneficiaries registered in Taiwan in the year 2000. For research purposes, the LHID2000 was systemically and randomly sampled by the National Health Research Institute from the Taiwanese population. The database included medical claims of all inpatient, outpatient, emergency department, and home care services. Before releasing the database, information related to personal identification was encrypted to protect patient privacy and data security.[21 22] National Health Research Institute approval was obtained prior to using the LHID2000 in this study. Diagnostic disease codes were derived using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This coding is considered highly reliable in the NHIRD, as insurance claims have been investigated by medical reimbursement specialists and the coding system has undergone peer review.[23] The study protocol we applied was approved by the Institutional Review Board of Tzu Chi Medical Center. The requirement for patient consent was waived owing to the retrospective nature of this study using de-identified secondary data.

Study population

The same database used in our previous study was employed here.[22] The database is comprised of adult patients (aged ≥20 years) with new-onset stroke occurring between 2000 and 2012; patients were identified by a primary discharge diagnosis of stroke (ICD-9-CM codes 430–437). The "index date" was defined as the date of the new-onset stroke diagnosis, while "index hospitalization" was defined as concurrent hospitalization for stroke. Exclusion criteria for this study were as follows: 1) history of stroke before the 2000–2012 study period; 2) history of pneumonia 1 year preceding the index date; 3) concurrent diagnosis of pneumonia during the index hospitalization; and/or 4) death during the index hospitalization.

Exposure to benzodiazepines

In Taiwan, BZDs are controlled by the Bureau of Controlled Drugs, and patients can only obtain such drugs through a doctor's prescription. We identified BZD prescriptions written after the index hospitalization using the prescription database in the LHID. The study population was then divided into BZD and non-BZD cohorts. The BZD cohort included patients who had used any BZDs after stroke during the follow-up period, while the non-BZD cohort was comprised of patients who were not prescribed BZDs post-stroke. To evaluate the effects of different BZD doses, we divided the BZD cohort into three subgroups using defined daily dose (DDD) methodology—a World Health Organization-recommended unit of measure employed to evaluate the prescribed amount of a drug for its main indication in an adult. Note that DDD methodology is widely used for the investigation of administrative pharmacy claim data.[21 23] Using this approach, we calculated the cumulative DDD (cDDD) by determining the sum of the dispensed DDD of all BZDs. This value was then employed to quantify BZD use during the study follow-up period. As such, the BZD cohort was divided into 1–90, 91–365, and >365 cDDD subgroups.

Outcome measures and sensitivity analysis

The main outcome of this study was defined as the occurrence of chronic-onset post-stroke pneumonia after index hospitalization, as identified by a discharge diagnosis of pneumonia (ICD-9-CM codes of 480–486). In order to increase the accuracy of this outcome, only pneumonia patients that required hospitalization were considered. According to previous research, chronic-onset post-stroke pneumonia is defined as pneumonia developing over 1 month after the incidence of stroke.[7] As the present study evaluated chronic-onset post-stroke pneumonia, cases of pneumonia diagnosed within 30 days of the stroke event were excluded. The identification of patients with pneumonia using ICD-9-CM coding in inpatient service has been previously validated and shows high accuracy.[24] All subjects were followed-up on, from the index date until the first occurrence of pneumonia, death, or until December 31, 2013. Death was defined as a patient withdrawn from the NHI program,[25] as previous studies have indicated that this is an accurate and reliable proxy for date of death.[26 27] Analyses stratified by age and sex were also performed.

In addition, to examine whether a diagnosis of pneumonia rendered in an outpatient service would influence our results, we performed a sensitivity analysis. For this analysis, pneumonia events were defined as those diagnosed during the follow-up period regardless of whether the diagnosis was rendered in an inpatient or outpatient service.

Covariates and propensity score matching

Baseline characteristics, such as demographic data, socioeconomic status, comorbidities, and clinical conditions, were obtained using reimbursement claims data and ICD-9-CM and procedure codes. A preexisting comorbidity was defined as a disease diagnosed at least one time during inpatient service or two times during outpatient visits within the year prior to the index date. The Charlson comorbidity index was calculated according to information related to preexisting comorbidities.[28] Baseline medication use was defined as any medication taken for at least 30 days over the course of the year preceding the index date. Information related to

stroke severity proxies was obtained based on the indicated clinical condition during the index hospitalization. Such information included diagnosis codes for hemiplegia and aphasia, operation/procedural codes for head surgery, mechanical ventilation, and utilization of the intensive care unit, as mentioned in our previous studies.[22 29] In addition, estimated National Institutes of Health Stroke Scale (NIHSS) scores were calculated to represent the severity of neurologic deficits, converting scores from a claims-based stroke severity index (SSI)—a measure specifically developed for use with Taiwan's NHIRD claims-based data—with a formula developed by Hsieh et al. (estimated NIHSS = 1.1722 × SSI − 0.7533).[30 31] The SSI has been validated in previous studies and is highly correlated with the NIHSS and consequent functional outcomes after stroke.[31-33] Additionally, some comorbidities may occur after stroke and also possibly cause a confounding effect. We therefore calculated an additional Charlson comorbidity index at the end point of follow-up, using the data on comorbidities from the year prior to the end-point date. Socioeconomic status was determined according to patient income and dwelling urbanization levels. Income, which was accessed based on NHI premiums, was classified into four levels (New Taiwan dollars ≥40,000, 20,000–39,999, 1–19,999, and financially dependent). Urbanization was classified into five levels, with level 1 corresponding to the most urbanized areas.[34] Detailed descriptions of income and urbanization levels have been described in our previous studies.[22 29]

In order to decrease the selection bias between groups, propensity score matching was performed to balance patient baseline characteristics, including age, sex, income level, urbanization level, comorbidities, Charlson comorbidity index, stroke severity proxies, and medication use (Table 1). A logistic regression model was used to calculate a propensity score, which estimated the probability of BZD use based on all baseline covariates for each BZD user and non-user. Using the method of nearest-neighbor matching without replacement (with a caliper width equal to 0.2 standard deviations of the propensity score logit), we matched each BZD user with a non-BZD user.[22 35 36]

Statistical analysis

Continuous variables between the BZD and non-BZD cohort were compared using independent *t*-tests, while categorical variables were compared using chi-squared tests. The Kaplan-Meier method was performed to estimate the risk of developing pneumonia and the log-rank test was used to compare differences between cumulative incidence curves. Univariate and multivariate Cox proportional hazards regression models were used to compute the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for developing pneumonia after stroke; all baseline characteristics listed in Table 1 were adjusted for when conducting the multivariate Cox proportional hazards regression models. To eliminate possible bias caused by competing mortality, modified Cox proportional hazards regression models were used with adjustment for competing risk events.[25 37] Differences were considered statistically significant at a two-sided probability value of <0.05. All statistical analyses were performed using Stata version 13 (Stata Corporation, College Station, TX, USA).

Patient and public involvement

Due to the present study having used de-identified secondary data, the patients and public were not directly involved in this study and the need for consent was waived.

Results

Demographic characteristics

After propensity score matching according to the baseline characteristics listed in Table 1, a total of 7516 patients with newly onset stroke were included in our study. Among these patients, 3758 received BZDs and were classified into the BZD cohort, while 3758 did not receive BZDs and were classified into the non-BZD cohort. Although most baseline characteristics were well-balanced after propensity score matching, significant differences were found regarding the baseline prevalence of sleep disorders and the proportion of patients using anti-hypertensive agents and anxiolytics; however, the actual between-group differences were minor (Table 1).

Risk of chronic-onset post-stroke pneumonia according to BZD use

During a mean follow-up of 4.4 years, 1027 patients in the BZD cohort (52.2/1000 person-years), compared to 478 patients in the non-BZD cohort (32.6/1000 person-years), developed pneumonia. A Kaplan-Meier analysis revealed a significantly higher cumulative incidence of pneumonia in the BZD than in the non-BZD cohort (log-rank test, $p < 0.0001$) (Figure 1). Cox proportional hazards regression models revealed that BZD use after stroke was associated with an increased risk of pneumonia in both the univariate (crude HR = 1.95, 95% CI = 1.75–2.17, $p < 0.001$) and multivariate models (adjusted HR [aHR] = 2.21, 95% CI = 1.97–2.48, $p < 0.001$) (Table 2).

Analyses according to different cumulative BZD doses

Patients in all three cDDD subgroups had a higher risk of developing pneumonia than did the non-BZD cohort. The aHRs for the 1–90, 91–365, and >365 cDDD subgroups were 2.28 (95% CI = 2.01–2.58; $p < 0.001$), 2.09 (95% CI = 1.77–2.47; $p < 0.001$), and 2.08 (95% CI = 1.72–2.52; $p < 0.001$), respectively (Table 3).

Analyses after stratification for age and sex

The association between BZD use and the risk of pneumonia development in stroke patients was further analyzed after stratification for age and sex (Table 4). Using this approach, we found a significantly greater risk of pneumonia in BZD users than in non-users in both age subgroups (<65 years old: aHR = 2.42, 95% CI = 1.84–3.17, $p < 0.001$; ≥65 years old: aHR = 2.11, 95% CI = 1.86–2.40, $p < 0.001$). Additionally, BZD users had an increased risk of pneumonia in both male (aHR = 2.46, 95% CI = 2.13–2.84, $p < 0.001$) and female (aHR = 1.83, 95% CI = 1.50–2.22, $p < 0.001$) subgroups (Table 4). Together, these results reveal that BZD use after stroke was associated with an increased risk of pneumonia regardless of age and sex.

Results of sensitivity analysis

In the sensitivity analysis, which considered the pneumonia event regardless of diagnosis in inpatient or outpatient service, BZD use was independently associated with increased risk of developing pneumonia (adjusted HR = 1.94, 95% CI = 1.77- 2.14, $p < 0.001$). The results for different cumulative doses of BZDs also revealed a pattern to our primary analyses. The detailed statistical values are shown in the Supplementary materials (Supplementary Table S1).

Discussion

This population-based propensity-matched retrospective cohort study investigated the association between BZD use and the risk of chronic-onset post-stroke pneumonia. We observed that patients prescribed BZDs post-stroke had a risk of developing pneumonia that was 2.21 times higher than that for patients who had not been prescribed BZDs. To the best of our knowledge, this is the first large-scale study to demonstrate an association between BZD use and the risk of chronic-onset post-stroke pneumonia over a long-term follow-up period.

Our results are consistent with those previously reported by studies that focused on the general population.[9-11] For example, previous observational studies found a 54 to 176% increase in the risk of pneumonia development in BZD users when compared to non-BZD users (relative risk or odds ratio: 1.54,[9] 1.86,[10] and 2.76 [11]). However, other observational studies have reported conflicting results, showing negative or nonsignificant relationships between BZD use and the risk of pneumonia.[14 16-18] For instance, a previous case-control study on participants aged ≥65 years old did not find a significant association between BZD use and pneumonia risk; however, only 87 BZD users were found among all of the pneumonia cases included in that study.[14] Another cross-sectional study using 30-, 60-, and 90-day windows revealed protective effects of BZDs on the risk of pneumonia, but was conducted over a relatively short study period and focused on the general population.[18]

Pneumonia is a significant complication in stroke patients owing to the increased risk of apparent aspiration and dysphagia-associated microaspiration, as well as stroke-induced immunodepression.[6 7 38] Acute-onset post-stroke pneumonia, which develops within 1 month of the stroke event, is mainly associated with apparent aspiration and stroke-induced immunodepression.[6 7] However, although apparent aspiration and immunodepression gradually attenuate following stroke recovery, the silent aspiration or microaspiration into the lower airways may still occur and cause chronic-onset post-stroke pneumonia.[7 39] BZDs are commonly used in stroke patients on account of the high prevalence of psychological

problems in stroke patients;[17 19 20] previous studies have indicated that BZDs may be associated with the increased risk of aspiration and depression of immune cells.[9-13] To the best of our knowledge, the only previous study to focus on the association between BZDs and pneumonia in stroke patients did not reveal a significant association between BZD use and the risk of pneumonia post-stroke; however, in that study, the follow-up period for identifying pneumonia was only 90 days post-stroke.[17] In contrast, the current study, which specifically focused on the chronic phase of post-stroke to evaluate pneumonia developed over 1 month after the stroke,[7] included a large sample size and long-term follow-up period (mean follow-up time, 4.4 years). The present study revealed a significantly increased risk of chronic-onset pneumonia in stroke survivors using BZDs (aHR = 2.21), even after carefully controlling for socioeconomic status, important comorbidities, stroke severity proxies, and concomitant medications. In addition, the subgroup analyses, which were performed according to cumulative BZD doses and stratified for age and sex, also revealed a similar pattern of results, further strengthening our findings. As pneumonia is one of the most common serious medical complications following stroke and can cause not only poor functional outcomes but also high mortality and financial burdens, we believe that our study addresses a knowledge gap regarding the clinical management of patients after stroke.

Although the exact biological mechanisms underlying the influence of BZDs on pneumonia remain unclear, some hypotheses have been reported. One previous animal study suggested that BZDs may negatively influence immune function via the activation of $GABA_A$ receptors on immune cells, thus interfering with macrophages/monocytes and impairing cytokine release, phagocytosis, and bacterial killing capabilities.[12] In addition, BZDs may increase the risk of aspiration by decreasing lower esophageal sphincter pressure, inducing the relaxation of muscles in the upper respiratory tract, and depressing the swallowing reflex, ultimately leading to pharyngeal dysfunction.[11 13 40] Further research is necessary to explore these postulated mechanisms.

The strengths of the present study include its large sample size, use of a nationwide population database, and the provision of sufficient power to evaluate the effect of BZDs on the risk of pneumonia development after stroke over a long-term follow-up period. The study design also provided better evidence in terms of epidemiology than previous studies that used case-control or cross-sectional designs. Moreover, performing propensity score matching before our analyses and then using multivariate Cox proportional hazard regression models with adjustment for competing mortality allowed us to rule out several important sources of bias and ensured that confounding factors were carefully controlled.

The following limitations of the present study should also be acknowledged. First, the claim-based database did not allow for the retrieval of certain clinical information (e.g., patient lifestyle and physical, psychiatric, or laboratory examination data). Although our study design ensured the control of several variables, unknown or unmeasured confounders could still exist. Second, by using de-identified claims, we could not obtain the patient details to analyze the medical history and identify exact mechanism of pneumonia; thus, we could not determine whether the pneumonia was caused by aspiration or not. Third, our analyses performed according to different cumulative BZD doses did not reveal an obvious dose-effect relationship. It is difficult to completely avoid an indication bias in observational studies that evaluate the effect of medication or intervention. Hence, the existence of unidentified residual confounders (i.e., the effect of the underlying etiologies needing BDZ prescription, other exposures, etc.) cannot be completely ruled out from the present study. Thus, further prospective clinical trials are necessary to address these possible biases and to determine the cause-and-effect relationship between post-stroke BZD use and the pneumonia risk. Finally, the accuracy of the diagnostic coding could not be directly confirmed due to the anonymity policy enforced in the NHIRD. However, only patients who were hospitalized under a primary diagnosis of stroke were included in our study population. The identification of stroke and pneumonia using ICD-9-CM coding in inpatient services has been previously

validated and shows high accuracy.[24 41 42] Additionally, the claims were routinely and randomly reviewed by the National Health Insurance Bureau to confirm the diagnostic accuracy. Given that hospitals and doctors in Taiwan are heavily fined in instances of misdiagnosis and coding errors, we feel confident in the validity of the criteria used for the inclusion of stroke and pneumonia cases in this study.

Conclusions

In summary, this population-based propensity-matched retrospective cohort study indicated an association between BZD use and an increased risk of chronic-onset post-stroke pneumonia. However, further large-scale prospective studies are needed to determine possible cause-effect relationships.

Contributors: Study conception and design: Shu-Man Lin, Huei-Kai Huang, and Ching-Hui Loh; acquisition of data: Shih-Hsien Yang and Huei-Kai Huang; analysis and interpretation of data: Shu-Man Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh; drafting of manuscript: Shu-Man Lin and Huei-Kai Huang; critical revision: Shu-Man Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh.

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Competing interests: The authors declare that no competing interests exist.

Ethics approval: The study was approved by the Institutional Review Board of Tzu Chi Medical Center (REC No. IRB104-131C).

Data sharing statement: All relevant data are within the paper. No additional data are available.

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Figure legends

Figure 1. Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

Table 1. Baseline characteristics of patients post-stroke in the BZD and non-BZD cohorts after propensity score matching

	BZD use				p value
	Yes (n = 3,758)		No (n = 3,758)		
	n	%	n	%	
Age (years)	66.2 ± 14.9		66.3 ± 14.7		0.941
Sex					0.267
Male	2,455	65.3	2,409	64.1	
Female	1,303	34.7	1,349	35.9	
Income level (NTD)					0.816
Financially dependent	1,123	29.9	1,125	29.9	
1–19,999	1,801	47.9	1,826	48.6	
20,000–39,999	522	13.9	516	13.7	
≥40,000	312	8.3	291	7.7	
Urbanization level					0.732
1 (Most urbanized)	974	25.9	985	26.2	
2	993	26.4	1,010	26.9	
3	791	21.0	744	19.8	
4	579	15.4	580	15.4	
5 (Least urbanized)	421	11.2	439	11.7	
Comorbidities					
Charlson comorbidity index	2.26 ± 1.50		2.27 ± 1.63		0.837
Hypertension	2,666	70.9	2,666	70.9	1.000
Diabetes mellitus	1,263	33.6	1,256	33.4	0.864
COPD	247	6.6	265	7.1	0.410
Asthma	114	3.0	112	3.0	0.893
Chronic kidney disease	180	4.8	198	5.3	0.342
Cirrhosis	200	5.3	207	5.5	0.721
Coronary artery disease	491	13.1	528	14.1	0.213
Congestive heart failure	192	5.1	202	5.4	0.605
Pneumoconiosis	6	0.2	7	0.2	0.781
Hyperlipidemia	1,096	29.2	1,080	28.7	0.684
Malignancy	188	5.0	176	4.7	0.519
Dementia	207	5.5	208	5.5	0.960
Depression	34	0.9	50	1.3	0.079
Parkinsonism	107	2.8	106	2.8	0.945

Epilepsy	24	0.6	26	0.7	0.777
Bipolar disorders	3	0.1	3	0.1	1.000
Alcohol related disorders	14	0.4	19	0.5	0.383
Substance use disorders	18	0.5	18	0.5	1.000
Schizophrenia	18	0.5	16	0.4	0.731
Anxiety	90	2.4	104	2.8	0.309
Sleep disorders	170	4.5	186	4.9	0.385
Charlson comorbidity index at the end point of follow-up	2.03 ± 1.79		2.13 ± 2.06		0.022
Stroke severity proxies					
Estimated NIHSS	8.0 ± 6.0		7.7 ± 5.8		0.061
ICU utilization	937	24.9	871	23.2	0.075
Mechanical ventilation	308	8.2	299	8.0	0.703
Hemiplegia	562	15.0	530	14.1	0.295
Aphasia	69	1.8	63	1.7	0.598
Neurosurgery	202	5.4	210	5.6	0.685
Use of medication					
Steroids	109	2.9	116	3.1	0.636
Anti-diabetic agents	795	21.2	821	21.8	0.465
Anti-hypertensive agents	1,676	44.6	1,715	45.6	0.366
Statins	319	8.5	332	8.8	0.594
Proton pump inhibitors	89	2.4	97	2.6	0.553
Anti-epileptics	70	1.9	82	2.2	0.325
Antiparkinsonian	92	2.4	90	2.4	0.881
Antipsychotics	76	2.0	85	2.3	0.473
Anxiolytics	246	6.5	286	7.6	0.072
Hypnotics and sedatives	156	4.2	180	4.8	0.180
Antidepressants	79	2.1	97	2.6	0.170

Continuous data expressed as mean ± standard deviation (SD) and categorical data expressed as number and percentage.

Abbreviations: BZD, benzodiazepine; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan dollars; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Risk of pneumonia after stroke among patients in the BZD and non-BZD cohorts

	BZD use	
	Yes	No
Patient numbers	3758	3758
Pneumonia cases	1027	478
Person-years	19680.1	14663.8
Incidence rate*	52.2	32.6
Univariate model		
Crude HR (95% CI)	1.95 (1.75–2.17)	1 (ref.)
p value	<0.001	
Multivariate model†		
Adjusted HR (95% CI)	2.21 (1.97–2.48)	1 (ref.)
p value	<0.001	

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

Table 3. Risk of pneumonia after stroke according to different cumulative BZD doses

Cumulative BZD doses	n	Pneumonia cases	Person-years	Incidence rate*	Univariate model		Multivariate model†	
					Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	3758	478	14663.8	32.6	1 (ref.)		1 (ref.)	
1–90 cDDDs	2507	702	11760.2	59.7	2.10 (1.87–2.36)	<0.001	2.28 (2.01–2.58)	<0.001
91–365 cDDDs	728	198	4216.6	47.0	1.84 (1.56–2.16)	<0.001	2.09 (1.77–2.47)	<0.001
>365 cDDDs	523	127	3703.4	34.3	1.47 (1.21–1.77)	<0.001	2.08 (1.72–2.52)	<0.001

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDDs, cumulative defined daily doses

Table 4. Risk of pneumonia after stroke in the BZD and non-BZD cohorts after stratification for age and sex

	BZD use				Non-BZD use				Univariate model		Multivariate model†	
	n	Pneumonia cases	Person-years	Incidence rate*	n	Pneumonia cases	Person-years	Incidence rate*	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Age												
<65	1599	221	10438.4	21.2	1626	77	7568.1	10.2	2.32 (1.79–3.00)	<0.001	2.42 (1.84–3.17)	<0.001
≥65	2159	806	9241.7	87.2	2132	401	7095.7	56.5	1.94 (1.72–2.18)	<0.001	2.11 (1.86–2.40)	<0.001
Sex												
Male	2455	721	12709.5	56.7	2409	278	9945.3	28.0	2.35 (2.04–2.69)	<0.001	2.46 (2.13–2.84)	<0.001
Female	1303	306	6970.6	43.9	1349	200	4718.5	42.4	1.39 (1.16–1.66)	<0.001	1.83 (1.50–2.22)	<0.001

*Per 1,000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

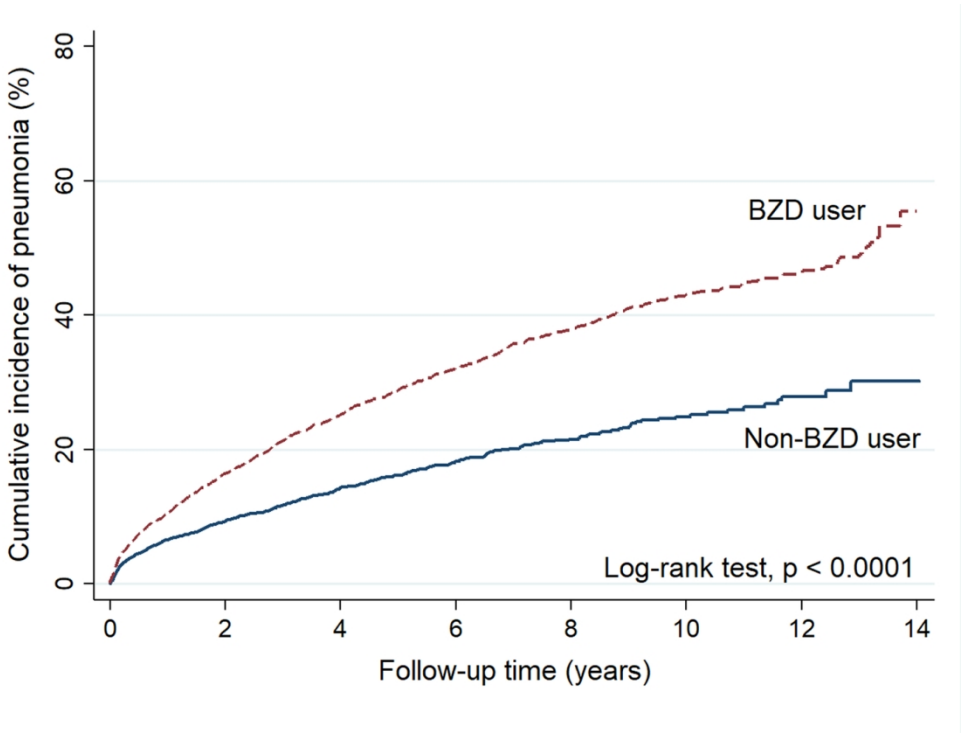

Figure 1. Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

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Supplementary Materials

Table S1. Sensitivity analysis of risk of contracting pneumonia after stroke according to BZD-use status

Cumulative BZD doses	Univariate model		Multivariate model†	
	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	1 (ref.)		1 (ref.)	
All BZD user	1.75 (1.60–1.91)	<0.001	1.94 (1.77–2.14)	<0.001
1–90 cDDDs	1.83 (1.66–2.02)	<0.001	1.96 (1.77–2.18)	<0.001
91–365 cDDDs	1.72 (1.50–1.98)	<0.001	1.89 (1.64–2.18)	<0.001
>365 cDDDs	1.45 (1.24–1.70)	<0.001	1.92 (1.63–2.25)	<0.001

For the sensitivity analysis, pneumonia events were defined as those diagnosed during the follow-up period regardless of whether the diagnosis was rendered in an inpatient or outpatient service.

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDDs, cumulative defined daily doses

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number in manuscript
✓ **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
✓ Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
✓ Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
✓ Study design	4	Present key elements of study design early in the paper	6-8
✓ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
✓ Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8-9 Table 1
✓ Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
✓ Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
✓ Bias	9	Describe any efforts to address potential sources of bias	8-10
✓ Study size	10	Explain how the study size was arrived at	6-7
✓ Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
✓ Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	8
Results			
✓ Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
✓ Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 p.11
		(b) Indicate number of participants with missing data for each	N/A

		variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	11
✓ Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2-4 p.11-12
✓ Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12 Table 1
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
✓ Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
✓ Key results	18	Summarise key results with reference to study objectives	13
✓ Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
✓ Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
✓ Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
✓ Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.