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Stroke and osteoporosis: a Taiwan cohort study

Li Zhang,¹ Zi-Hao Zhang,^{2,3} Qing-Rui Wang,⁴ Ying-Ju Su,⁵ Ying-Yi Lu,^{6,7,8}
Cong-Liang Zhang,⁹ Hung-Pei Tsai ,^{10,11} Chieh-Hsin Wu ,^{10,12}

For numbered affiliations see end of article.

Correspondence to

Dr Chieh-Hsin Wu, Kaohsiung 80756, Taiwan; wujoey@gmail.com

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ABSTRACT

Background Osteoporosis and stroke are major health problems that have potentially overlapping pathophysiological mechanisms. The aim of this study was to estimate osteoporosis risk in Taiwan patients who had a stroke.

Method This study retrieved data contained in the Taiwan National Health Insurance Research Database for a population-based sample of consecutive patients either hospitalised for stroke or treated for stroke on an outpatient basis. A total of 7550 newly diagnosed patients who had a stroke were enrolled during 1996–2010. Osteoporosis risk in these patients was then compared with a matched group of patients who had not had a stroke randomly selected from the database at a ratio of 1:4 (n=30 200). The relationship between stroke history and osteoporosis risk was estimated with Cox proportional hazard regression models.

Results During the follow-up period, osteoporosis developed in 1537 patients who had a stroke and in 5830 patients who had not had a stroke. The incidence of osteoporosis for cohorts with and without stroke was 32.97 and 14.28 per 1000 person-years, respectively. After controlling for covariates, the overall risk of osteoporosis was 1.82-fold higher in the stroke group than in the non-stroke group. The relative osteoporosis risk contributed by stroke had apparently greater impact among male gender and younger age groups.

Conclusion History of stroke is a risk factor for osteoporosis in Taiwan. Much attention to stroke-targeted treatment modalities might minimise adverse outcomes of osteoporosis.

INTRODUCTION

Currently, 15 million persons worldwide suffer a stroke every year.¹ In the adult population in the USA, stroke is the most common cause of disability and the fourth most common cause of mortality.^{2,3} In the USA, the prevalence of stroke and its cost will undoubtedly rise as the aged population increases. Meanwhile, the stroke burden and its mortality rates are especially higher in Asia than in Western Europe, the Americas and Australasia.⁴ Asia is the most populous continent with an estimated 60% of the world's population and the highest incidence rates of stroke are in Japan and Taiwan.⁴ In Taiwan, stroke is the leading cause of complex disability and the third most common cause of death.⁵ Although the prevalence is nearly twofold higher in men than in women, women tend to have poor outcomes.^{6,7} Compared with haemorrhagic strokes, ischaemic stroke occurs more frequently.⁵ The disabilities caused by stroke may make survivors unable to work, and can cause serious financial problems.

Stroke-related impairments and inactivity are known to accelerate development of osteoporosis and the need for bone mass removal.⁸

Osteoporosis, which is a systemic metabolic bone disease that can have multiple causes, is characterised by a progressive loss of bone mass and microarchitecture resulting in a high fracture risk.^{9–10} In Taiwan, there are approximately 500 000 people aged over 65 years old diagnosed with osteoporosis, and 25% of them have experienced a spine or hip fracture.¹¹ Whereas osteoporosis is usually a major complication of stroke, both stroke and osteoporosis are highly debilitating diseases. In comparison with age-related osteoporosis, bone loss secondary to metabolic diseases, nutritional problems and drug-related factors, osteoporosis after stroke is known to occur more frequently on the paretic side and is more likely to involve the upper rather than lower extremities.¹² Osteoporosis may make fragile bones, leading to higher mortality or morbidity rates and a lower quality of life.¹³

However, no studies involved in Asian population have comprehensively investigated the extent of decrease in bone mineral density (BMD) after stroke and the causes of rapid bone loss. Additionally, although many studies have examined osteoporosis–stroke relationships in western populations, gender differences in these relationships remain unclear. Moreover, no studies have investigated osteoporosis–stroke relationships in an adult Asian population. Therefore, this study analysed this relationship in a Taiwan population by collecting representative administrative data from the Taiwan National Health Insurance Research Database (NHIRD).

MATERIALS AND METHODS

Database

The mandatory health insurance programme, Taiwan National Health Insurance (NHI) project, is the only payer system launched on 1 March 1995, which covers nearly 99% of the 23.74 million Taiwan residents.^{14–15} The National Health Research Institutes created the NHIRD for medical research. This database collected administrative and health claims data through the NHI programme. It comprised complete information on inpatient care, outpatient visit and contract pharmacies. It provides scholars with clinical information, including records on patients' gender, birth date, medical services registration and medication prescriptions. In this paper, we used the subset of the NHIRD, Longitudinal Health Insurance Database 2010 (LHID2010), which is a subset of the NHIRD comprising patient data from 1996 to 2010. The LHID2010 contains



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data on 1 000 000 randomly sampled beneficiaries from the original NHIRD enrolled in 2010. The large sample size database provides an opportunity to find out the risk of osteoporosis among patients who had a stroke. The diseases criteria were defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Ethical approval

In this study, we used the insurance reimbursement claims data retrieved from Taiwan's NHIRD. We conducted the study in accordance with the Declaration of Helsinki.

Study population

A total 7550 patients aged 50 years and older diagnosed with stroke (ICD-9-CM code 430–436) between 1996 and 2010 were included in our study cohort. For data accuracy, we only included cases if they obtained ≥ 2 stroke diagnoses during outpatient visits or ≥ 1 diagnosis in inpatient care. The index date was designated as the first date of clinical visit for stroke. Procedures of craniotomy or craniectomy were evaluated as severity of stroke. Stroke subtypes were classified into haemorrhagic stroke (ICD-9-CM codes 430–432; 430 subarachnoid haemorrhage, 431–432 intracerebral and other intracranial haemorrhage),^{16 17} ischaemic stroke (ICD-9-CM codes 433–436 excluding 433.x0).^{18–20} Individuals with osteoporosis identified with a history of osteoporosis (ICD-9-CM code 733.0 or 733.1) or osteoporotic fractures, including vertebral fractures (ICD-9-CM code 805.2–805.9), humeral fracture (ICD-9-CM code 812), wrist fractures (ICD-9-CM code 813) and hip fractures (ICD-9-CM code 820)²¹ diagnosed before the index date, those with missing information and those aged younger than 50 years were excluded. To enhance the power of statistical tests and to ensure that the number of osteoporosis cases was sufficient for stratified analyses, the ratio of stroke to patients who had not had a stroke was 1:4.

We retrieved the non-stroke subjects for comparison cohort from the remaining insured people among LHID2010. We randomly selected 30 200 comparison subjects (four comparison subjects every patient) matched with the patients who had a stroke in terms of age, sex and index year, the year of stroke diagnosis. Moreover, we assured that none of the selected comparison subjects had received a diagnosis of osteoporosis prior to the index date. As a result, 30 200 non-stroke subjects were identified.

Outcome and comorbidities

The patients in both the stroke and non-stroke cohorts were followed up until they were diagnosed with osteoporosis or withdrawal from insurance or till the end of 2010. The baseline comorbidity histories of hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidaemia (ICD-9-CM code 272), chronic kidney disease (ICD-9-CM code 582, 583, 585, 586 and 588), chronic liver disease (ICD-9-CM code 456, 571 and 572), chronic pulmonary disease (ICD-9-CM code 490–496), hyperthyroidism (ICD-9-CM code 242), depression (ICD-9-CM code 296.2, 296.3, 300.4 and 311) were identified according to diagnoses in the claims records data. Besides, the use of oral corticosteroids or clopidogrel or coumadin or aspirin was also analysed.

Statistical analysis

The distributions of categorical demographics and clinical characteristics between the stroke cohorts and non-stroke cohorts

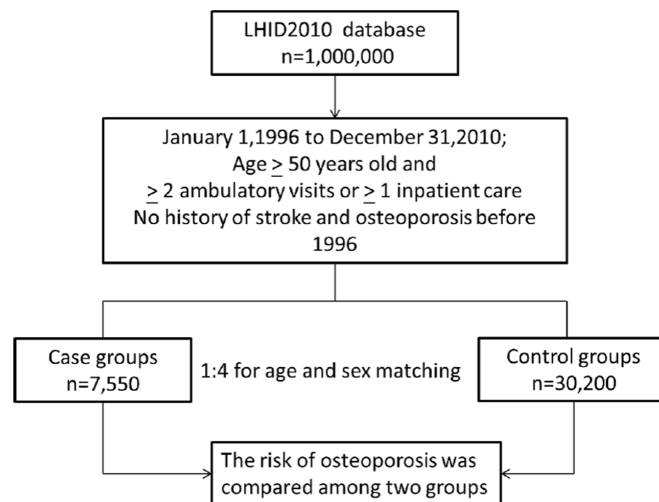


Figure 1 Flow diagram of the present study from the National Health Insurance Research Database in Taiwan. LHID, Longitudinal Health Insurance Database.

were compared using the χ^2 test. The Student's t-test and Wilcoxon rank-sum test were used as appropriate to examine the differences in mean age and follow-up time (years) between the two cohorts. The Kaplan-Meier method was used to estimate cumulative incidence, and the differences between the curves were tested using two-tailed log-rank test. Incidence rates of osteoporosis were estimated in 1000 person-years and compared in both cohorts. Univariable and multivariable Cox proportional hazard regression models are used to investigate the HR and 95% CI for osteoporosis if the proportional hazards assumption was satisfied. The multivariable Cox models were adjusted for age, sex and relevant comorbidities and medication. A two-tailed p value of <0.05 was considered statistically significant. All data processing and statistical analyses were performed using Statistical Analysis Software, V.9.4.

RESULTS

Characteristics of patients with and without stroke

Of the 37 750 enrolled patients between January 1996 and December 2010, 7550 were categorised as case (stroke) groups and 30 200 were categorised as the control (non-stroke) groups (figure 1).

Table 1 shows the demographic characteristics and comorbidity status in these two cohorts. As shown in table 1, the mean age was matched between the two cohorts, with 66.3 ± 9.4 years in the non-stroke cohort and 66.4 ± 9.3 years in the stroke cohort. Most patients were 60–69 years of age (35.02%), followed by 50–59 years of age (28.86%). The patients with stroke were more likely to develop comorbidities than the non-stroke group including hypertension (92.03% vs 55.20%, $p < 0.001$), diabetes mellitus (51.50% vs 27.67%, $p < 0.001$), hyperlipidaemia (65.25% vs 44.92%, $p < 0.001$), chronic kidney disease (27.74% vs 12.86%, $p < 0.001$), chronic liver disease (42.66% vs 35.86%, $p < 0.001$), chronic pulmonary disease (63.54% vs 43.64%, $p < 0.001$), hyperthyroidism (4.95% vs 3.93%, $p < 0.001$), depression (21.35% vs 9.22%, $p < 0.001$). Moreover, there was higher prevalence of use of corticosteroids (15.25% vs 7.90%, $p < 0.001$), clopidogrel (21.51% vs 3.18%, $p < 0.001$), coumadin (1.68% vs 0.26%, $p < 0.001$), aspirin (40.03% vs 10.49%, $p < 0.001$) in patients with stroke compared with those without stroke.

Table 1 Demographic characteristic of patients with and without stroke in Taiwan

Variables	Stroke		P value
	Yes n=7550	No n=30 200	
Osteoporosis patients, n (%)	1537 (20.36)	5830 (19.30)	<0.038
Period of developing osteoporosis median (IQR), years	3.2 (1.4–6.1)	6.5 (4.2–10.0)	<0.001
Age mean (SD), years	66.4 (9.3)	66.3 (9.4)	0.408
Age group, n (%)			
50–59	2179 (28.86)	8716 (28.86)	
60–69	2644 (35.02)	10576 (35.02)	
70–79	2148 (28.45)	8592 (28.45)	
≥80	579 (7.67)	2316 (7.67)	1.000
Sex, n (%)			
Males	4624 (59.69)	18496 (59.69)	
Females	3123 (40.31)	12492 (40.31)	1.000
Comorbidity, n (%)			
Hypertension	6498 (92.03)	16669 (55.20)	<0.001
Diabetes mellitus	3888 (51.50)	8355 (27.67)	<0.001
Hyperlipidaemia	4926 (65.25)	13566 (44.92)	<0.001
Chronic kidney disease	2094 (27.74)	3884 (12.86)	<0.001
Chronic liver disease	3221 (42.66)	10830 (35.86)	<0.001
Chronic pulmonary disease	4797 (63.54)	13178 (43.64)	<0.001
Hyperthyroidism	374 (4.95)	1188 (3.93)	<0.001
Depression	1612 (21.35)	2784 (9.22)	<0.001
Medication, n (%)			
Oral corticosteroids*	1151 (15.25)	2386 (7.90)	<0.001
Clopidogrel	1624 (21.51)	961 (3.18)	<0.001
Coumadin	127 (1.68)	80 (0.26)	<0.001
Aspirin	3022 (40.03)	3167 (10.49)	<0.001

*Oral prednisolone equivalent to 5 mg/day.

A total 1537 of 7550 patients who had a stroke (20.36 %) had osteoporosis during a median observation time of 3.2 years (IQR=1.4–6.1). The incidence of osteoporosis was significant higher ($p<0.0001$) than that in the control group, 5830 persons among the 30200 age and sex-matched control (19.38 %) during a median observation time of 6.5 years (IQR=4.2–10.0). The osteoporosis development period was significant faster in the stroke group (3.2 years) compared with the control group (6.5 years) during the following periods.

Incidence and risk of osteoporosis

Table 2 shows the incidence densities and HRs of osteoporosis at different gender, age. During follow-up period, 1537 patients with stroke (20.36%) and 5830 non-stroke participants (19.30%) developed osteoporosis. The incidence of osteoporosis for stroke group was 32.97 per 1000 person-years and that for non-stroke group was 14.28 per 1000 person-years. The overall risk of osteoporosis was 1.82-times greater in the stroke than in the comparison group after adjusting for age, sex, related comorbidities of hypertension, hyperlipidaemia, diabetes mellitus, chronic kidney disease, chronic pulmonary disease, chronic liver disease, hyperthyroidism, depression and medication use such as oral corticosteroids, clopidogrel, coumadin and aspirin.

The sex-specific analyses showed that women had a greater incidence of osteoporosis than men in both cohorts (57.49 vs 18.19 per 1000 person-years for stroke cohorts; 29.03 vs 5.99 per 1000 person-years for non-stroke cohorts). However, the relative risk of osteoporosis in patients who had a stroke compared with patients who had not had a stroke showed a relatively greater impact in men than women (HR=2.80 vs 1.55, P for interaction <0.001). Besides, incidence of osteoporosis was consistently higher in the stroke group at different age and the incidence rate increased with age. But the relative risk of osteoporosis in patients who had a stroke compared with patients who had not had a stroke showed the more pronounced risk in the younger-age group (HR=2.79, 95% CI 2.42 to 3.22, $p<0.001$, P for interaction <0.001).

The Kaplan-Meier curve of the cumulative incidence of osteoporosis in patients with and without stroke after 15 years of follow-up is shown in figure 2. The 1-year, 5-year, 10-year, 15-year actuarial rates of osteoporosis were 4.00%, 15.82%, 27.47%, 35.04% among patients who had a stroke and 0.04%, 7.02%, 14.45%, 19.30% among controls, respectively.

Table 3 shows different types of stroke associated with the relative risks and HR of osteoporosis. Compared with the non-stroke cohorts, patients with haemorrhagic stroke were 2.06-fold more likely to develop osteoporosis (95% CI 1.83 to 2.33) and patients with ischaemic stroke were 1.77-fold more likely to develop osteoporosis (95% CI 1.65 to 1.89). In addition, whether patients who had a stroke have received surgery or not, the risk of development of osteoporosis was higher than non-stroke cohorts.

Table 2 Incidence and HRs of osteoporosis by demographic characteristics among patients with or without stroke

Variables	Patients with stroke			Patients without stroke			Compared with non-stroke group		P value¶
	Osteoporosis	PY	Rate†	Osteoporosis	PY	Rate†	IRR (95% CI)‡	Adjusted HR (95% CI)§	
All	1537	46622.48	32.97	5830	408189.50	14.28	2.31 (2.18 to 2.44)***	1.82 (1.71 to 1.94)***	
Gender									
Men	529	29088.03	18.19	1567	261343.15	5.99	3.03 (2.75 to 3.35)***	2.80 (2.49 to 3.16)***	<0.001
Women	1008	17534.45	57.49	4263	146846.35	29.03	1.98 (1.85 to 2.12)***	1.55 (1.44 to 1.68)***	
Stratify age									
50–59	303	14289.87	21.20	696	125926.86	5.53	3.84 (3.35 to 4.39)***	2.79 (2.42 to 3.22)***	<0.001
60–69	608	17536.24	34.67	2078	141367.58	14.69	2.36 (2.15 to 2.58)***	1.77 (1.61 to 1.95)***	
>70	626	14796.37	42.31	3056	140895.06	21.69	1.95 (1.79 to 2.13)***	1.61 (1.47 to 1.76)***	

*** $p<0.001$.

†Incidence rate in per 1000 person-years.

‡IRR in per 1000 person-years.

§Model adjusted for age, sex, relevant comorbidities and medication.

¶P value for interaction.

IRR, incidence rate ratio; PY, person-years.

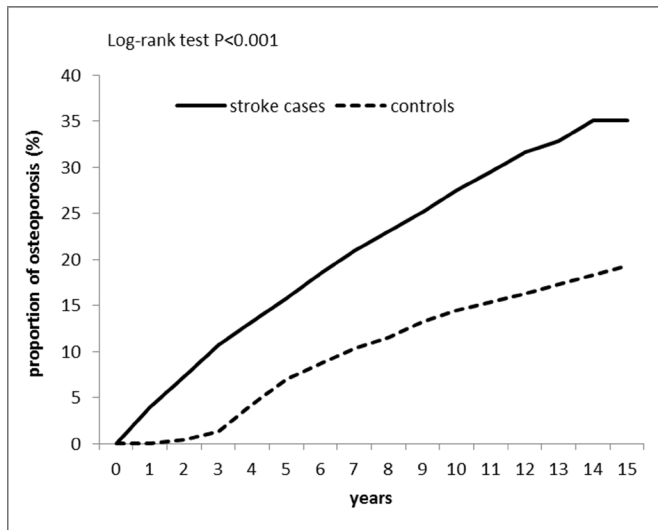


Figure 2 Cumulative incidence of osteoporosis for adult patients with stroke and the general population control cohort.

Table 4 shows that Cox regression analysis highlighted several risk factors for osteoporosis in the stroke group: female gender, older age, chronic pulmonary disease, chronic liver disease, depression and corticosteroids use.

DISCUSSION

After adjusting for comorbidities, overall osteoporosis risk was 1.82-fold higher in the stroke group compared with the non-stroke group. Notably, age and sex-specific analyses further showed stroke had a significantly greater impact on osteoporosis risk in men compared with women and the younger age compared with older age. Comparisons with non-stroke cohorts showed that haemorrhagic patients who had a stroke had a 2.06-fold higher osteoporosis risk whereas ischaemic patients who had a stroke had a 1.77-fold higher osteoporosis risk. Osteoporosis risk factors observed in the stroke cohort were old age, female gender, chronic pulmonary disease, chronic liver disease, depression and the use of corticosteroids.

Poststroke osteoporosis risk factors reported in the literature are inconsistent. However, many studies agree that risk factors include advanced age and underuse of limbs after stroke and therefore hip fracture.^{22,23} Another reported risk factor for post-stroke osteoporosis is female gender. In del Puente *et al*, a study of 48 hemiplegic subjects (31 men, 17 women in menopause) consecutively admitted for stroke over a 9-month period

Table 4 Cox regression model: significant predictors of osteoporosis after stroke (n=7550)

Variables	Adjusted HR*	95% CI	P value
Female	3.16	2.84 to 3.52	<0.001
Age (in 10-year interval)	1.31	1.23 to 1.38	<0.001
Chronic pulmonary disease	1.38	1.23 to 1.56	<0.001
Chronic liver disease	1.28	1.15 to 1.41	<0.001
Depression	1.31	1.17 to 1.46	<0.001
Corticosteroids use	1.32	1.17 to 1.49	<0.001

*Model adjusted for age, sex, relevant comorbidities and medication.

revealed that women had higher bone loss in the paralysed limb compared with men.²² Our study showed old age and female gender increased osteoporosis incidence in the stroke cohort.

Interestingly, our population-based cohort study of patients who had a stroke revealed that osteoporosis risk contributed by stroke compared with non-stroke group was significantly greater among male gender and young age. Furthermore, the Korean National Health and Nutrition Examination Survey of 3806 elderly subjects (1951 men and 1855 women) in 2008 and 2010 showed that, compared with males with no history of stroke, males with a history of stroke had a higher prevalence of osteoporosis, a higher prevalence of osteoporosis and a lower BMD in the total hip and femoral neck.²⁴

Our study also showed that, compared with the non-stroke cohorts, patients with haemorrhagic stroke had a 2.06-fold higher osteoporosis risk (95% CI 1.83 to 2.33), and patients with ischaemic stroke had a 1.77-fold higher osteoporosis risk (95% CI 1.65 to 1.89).¹² Additional poststroke osteoporosis risk factors include brain infarction and the use of anticoagulants for treating ischaemic stroke. For example, Sato *et al*²⁵ reported a larger BMD reduction in hemiplegic patients who had a stroke treated with warfarin compared with hemiplegic patients who had a stroke who did not take anticoagulants. In the group treated with warfarin, bone loss probably resulted from vitamin K-1 deficiency, which then reduced serum bone Gla protein.

Several issues should be considered when interpreting these results. First, we did not collect data for some osteoporosis risk factors such as low body mass index and vitamin D deficiency. Second, this analysis of stroke survivors was subject to selection bias. Nearly all patients who had a stroke in Taiwan visited medical care service unless patients with very mild symptoms or who had died before diagnosis did not.²⁶ Only people who seek medical care services were identified in our analysis; thus, underestimated risk of osteoporosis in stroke

Table 3 Incidence rates and HRs of osteoporosis risk in patients with different types of stroke

Variables	Osteoporosis	PY*	Rate†	IRR (95% CI)‡	Adjusted HR (95% CI)§
Without stroke	5830	408 189.50	14.28	1.00 (reference)	1.00 (reference)
Stroke type					
Haemorrhagic	303	9446.10	32.08	2.25 (2.00 to 2.52)***	2.06 (1.83 to 2.33)***
Ischaemic	1234	37 176.39	33.19	2.32 (2.19 to 2.47)***	1.77 (1.65 to 1.89)***
Surgery					
Non-received	1494	44 964.80	33.23	2.33 (2.19 to 2.46)***	1.81 (1.69 to 1.94)***
Received	43	1657.68	25.94	1.82 (1.35 to 2.45)***	2.08 (1.54 to 2.81)***

***p<0.001.

†Incidence rate in per 1000 person-years.

‡IRR in per 1000 person-years.

§Model adjusted for age, sex, relevant comorbidities and medication.

IRR, incidence rate ratio; PY, person-years.

cohort is possible.^{27,28} A third limitation is the potential for misclassification bias and unknown data accuracy since this cohort study analysed administrative data for patients who had been diagnosed by their physicians. The osteoporosis was determined only by claims because we could not obtain reliable information on BMD, which causes underestimation of osteoporosis. In addition, the claims data were collected for insurance reimbursement rather than research. Therefore, no available data regarding direct measurements of stroke severity to estimate the association with osteoporosis was also mentioned.²⁹ However, structured reviews have demonstrated high reliability and high validity in previous studies of administrative data.^{16–19,30} Notably, the validity of our results is increased by the structured methods used to collect data contained in the Taiwan NHIRD. Finally, despite our choice of a well-matched stroke control population and the additional use of random matching methods, we could not completely eliminate the residual risk of confounding effects caused by imbalance in baseline variables or imbalance in unmeasured confounders such as frailty. Despite these limitations, this analysis of detailed administrative data, including long-term follow-up data, for a large, population-based sample of patients who had a stroke is expected to provide useful valid data for osteoporosis risk after stroke through Cox proportional hazard model.

In summary, this study of a population of patients who had a stroke in Taiwan revealed a higher osteoporosis risk compared with a control group of patients without stroke. Poststroke osteoporosis was apparently important among male gender and young age groups. Since measuring BMD is an easily performed and non-invasive way to evaluate osteoporosis, alerting physicians to this association may improve early identification of osteoporosis in patients who had a stroke, mostly in patients with ischaemic insults.

Main messages

- ▶ Patients initially diagnosed with stroke have a high risk for developing osteoporosis.
- ▶ Both patients with haemorrhagic and ischaemic stroke tend to have osteoporosis.
- ▶ This study analyses the contribution of age and gender in osteoporosis risk in an Asian population from the Taiwan National Health Insurance Research Database.

Current research questions

- ▶ Does the type of stroke correlate with osteoporosis in Taiwan patients?
- ▶ How does gender affect patients who had a stroke with osteoporosis?
- ▶ Do younger patients who had a stroke have higher osteoporosis risks?

What is already known on the subject

- ▶ Both stroke and osteoporosis are worldwide health burden.
- ▶ The association between stroke and osteoporosis is bidirectional.

Author affiliations

¹Department of Neurosurgery, The Affiliated Zhangjiagang Hospital of Soochow University, Zhangjiagang, Jiangsu, P.R. China

²Department of Neurosurgery, The No.7 People's Hospital of Hebei Province, Dingzhou, Hebei, P.R. China

³Department of Neurosurgery, the Affiliated Second Hospital of Hebei University of Chinese Medicine, Shijiazhuang, Hebei, P.R. China

⁴Department of Neurosurgery, Qinghe County Central Hospital of Hebei Province, Qinghe, Hebei, P.R. China

⁵Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

⁶Department of Dermatology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

⁷Department of Nursing, Shu-Zen Junior College of Medicine and Management, Kaohsiung, Taiwan

⁸Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

⁹Department of Cardiology, Hebei Quyang Renji Hospital, Quyang, Hebei, P.R. China

¹⁰Division of Neurosurgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

¹¹Division of Neurosurgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

¹²Department of Surgery, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Contributors Z-HZ and LZ were equal contributors in this study. Y-JS and Q-RW were equal contributors in this study. The authors' individual contributions are outlined as follows. Substantial contributions to conception and design: LZ, Q-RW, Z-HZ, Y-JS, Y-YL, C-LZ and C-HW. Drafting and revising the article critically for important intellectual content: Q-RW, LZ, Y-JS, Z-HZ, H-PT and C-HW. Final approval of the version to be published: Z-HZ, LZ and C-HW.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article.

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ORCID iDs

Hung-Pei Tsai <http://orcid.org/0000-0001-9170-6268>

Chieh-Hsin Wu <http://orcid.org/0000-0001-5116-8004>

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