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ORIGINAL ARTICLE

Herpes zoster and the risks of osteoporosis and fracture: a nationwide cohort study

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Abstract

This study aimed to investigate the association between herpes zoster (HZ) and the risks of osteoporosis and fracture. We conducted a nationwide retrospective cohort study using the National Health Insurance Research Database of Taiwan. The study enrolled 63,786 patients: 31,893 diagnosed with HZ between 2000 and 2012 were included in the HZ cohort, and 31,893 matched controls without HZ were included in the non-HZ cohort, with 1:1 exact matching for age, sex, and index year. Hazard ratios (HRs) were calculated for the risks of osteoporosis and fracture according to the HZ status using the Cox proportional hazards regression models. During a mean follow-up period of 6.0 years, 5597 and 4639 patients in the HZ and non-HZ cohorts, respectively, developed osteoporosis or fractures (incidence rate: 29.8 vs. 23.8 per 1000 person-years). HZ diagnosis was significantly associated with an elevated risk of developing osteoporosis or fracture (adjusted HR [aHR] = 1.20, $p < 0.001$). On analyses for each individual event, the HZ cohort had significantly increased risks for all events, including osteoporosis (aHR = 1.32, $p < 0.001$), hip fracture (aHR = 1.34, $p < 0.001$), vertebral fracture (aHR = 1.38, $p < 0.001$), and other fractures (aHR = 1.10, $p < 0.001$) compared with the non-HZ cohort. Patients with postherpetic neuralgia had especially higher risks of osteoporosis and fracture. Age- and sex-stratified analyses also revealed similar patterns. In conclusion, HZ was independently associated with an increased risk of osteoporosis and fracture. Further studies are required to investigate its underlying mechanisms.

Keywords Herpes zoster · Postherpetic neuralgia · Osteoporosis · Fracture · Cohort study · Hip fracture · Vertebral fracture

Introduction

Osteoporosis and fracture are major public health issues in the aging population. Osteoporosis, a skeletal disease characterized by low bone mass and impaired bone strength and microarchitecture, significantly increases the risk of fractures and further causes morbidity, mortality, and socioeconomic burden [1–3].

Herpes zoster (HZ), a reactivated condition of varicella zoster virus infection, is a latent neurotrophic viral disease characterized by vesicular eruptions in the dermatome. After vesicular eruptions, postherpetic neuralgia (PHN), a neuropathic pain syndrome that persists or develops after the dermatomal rash heals, sometimes occurs. The PHN is the most frequent and debilitating complication of HZ [4, 5].

Although the relationship between osteoporosis and HZ has been discussed decades ago, evidence on this association remains limited [6–8]. The only recent large-scale observational study, which included patients aged 20–49 years, has demonstrated the association between HZ and increased osteoporosis risks [9]. However, in clinical practice, osteoporosis is mainly diagnosed among patients aged older than 50 years [10], who were excluded from that previous study [9]. Moreover, to the best of the authors' knowledge, thus far, the association between HZ and the risk of developing fractures has not been reported previously.

Shu-Man Lin, Chih-Yung Wang and Ying-Yu Chen contributed equally to this work.

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Therefore, we conducted a nationwide retrospective cohort study to investigate the association between HZ and the risks of osteoporosis and fracture.

Methods

Data sources

Taiwan's National Health Insurance (NHI) program, which was launched in 1995, is a single-payer mandatory enrollment insurance program administered by the government. The Taiwanese health system is characterized by its accessibility, comprehensive population coverage, and low costs and has a national health insurance databank for planning, monitoring, and evaluating health services [11]. NHI of Taiwan offers a comprehensive benefits package; almost all services are covered by NHI, from dental care to parturition, from Western medicine to traditional Chinese medicine, and from preventive services to elderly home care. In addition, medications are covered [11, 12]. Out-of-pocket expenditures are limited, but every service is accompanied by a co-payment. The NHI covers more than 99% of the Taiwanese population. For research purposes, the National Health Research Institute (NHRI) of Taiwan established a subset of National Health Insurance Research Database, called the Longitudinal Heath Insurance Database (LHID), which included 1 million people who were randomly and systemically sampled from the total of 23.8 million NHI beneficiaries in Taiwan. We conducted this nationwide retrospective cohort study using the LHID, which has the registry of beneficiaries and all medical claims for services of outpatient, inpatient, and emergency departments from 1999 to 2013. Before releasing the database by NHRI, the subjects' personal identifiers were encrypted to protect patient privacy and for data security. The Institutional Review Board of Tzu Chi Medical Center approved this study protocol (REC No.: IRB107-60C).

Study population

The study population included an HZ cohort (case cohort) and a non-HZ cohort (control cohort). Patients were included in the HZ cohort if they had been diagnosed with HZ between 2000 and 2012 in the LHID. The definition of HZ diagnosis is at least one time inpatient or two times outpatient diagnosis during the study period using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code of 053.x, and the earliest date of diagnosis for HZ was defined as the index date. Those who had been diagnosed with HZ before 2000 were excluded, to increase the likelihood of identifying newly diagnosed cases; those who had developed osteoporosis or any fractures before the index date were also excluded because these were our primary outcomes. To construct the non-HZ cohort (control cohort), each HZ patient was matched with a non-HZ patient by 1:1 exact matching in terms of age, sex, and index year using the LHID. Any subject in the non-HZ cohort with a previous diagnosis of osteoporosis or fractures was also excluded, similar to that in the HZ cohort. The index date for each control (non-HZ patient) was assigned as the same index date of their matched case (HZ patient). In addition, to evaluate whether PHN influence the outcomes, the HZ cohort was further divided into two groups, the PHN group and the non-PHN group. The PHN group included HZ patients who had been diagnosed with PHN (ICD-9-CM codes 053.12 and 053.19). Those who had not been diagnosed with PHN were classified as the non-PHN group.

Outcome measures

Any new diagnosis of osteoporosis or fractures (ICD-9-CM codes 733.0, 733.1, and 800.x–829.x) was defined as the primary outcome. We also analyzed each event as our individual study outcome, including osteoporosis (ICD-9-CM codes 733.0, 733.1), hip fracture (ICD-9-CM codes 820.x and 733.14), vertebral fracture (ICD-9-CM codes 805.x, 806.x, and 733.13), and other fractures (ICD-9-CM codes 800.x–804.x, 807.x–819.x, and 821.x–829.x). All study subjects were followed up from the index date until the occurrence of the study outcome, death, withdrawal from the NHI program, or December 31, 2013.

Covariates

Baseline characteristics and clinical information that were considered as potential confounders were retrieved according to the ICD-9-CM, procedure, and prescription codes from the reimbursement claims in the LHID. Preexisting comorbidities were defined as diseases that required to be diagnosed by at least one inpatient service or by two outpatient services in the 1-year period before the index date; baseline medications were defined as drugs used for at least 30 days within the 1-year period before the index date. Charlson comorbidity index, which can represent the overall comorbidity status and has been widely used in epidemiologic and clinical studies, was also calculated [13].

Socioeconomic status was assessed using the income and urbanization levels of the study subjects. Income level was estimated according to the income-related NHI premiums and was categorized into four levels (New Taiwan dollars ≥ 40,000, 20,000–39,999, 1–19,999, and financially dependent). Urbanization level, which was categorized into five levels (with level 1 as the most urbanized areas), was determined by the place of residence of the study subjects according to the information of registry of beneficiaries in the LHID. More detailed descriptions for how income and urbanization levels were accessed have been provided in previous studies [14, 15].

Statistical analysis

Continuous variables were compared using independent t tests and categorical variables, by χ^2 tests. The cumulative incidences of outcomes were calculated by Kaplan–Meier methods, and the curves were compared by log-rank tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) for developing osteoporosis and fractures were calculated using univariate and multivariate Cox proportional hazards regression models. Statistical significance was considered at a two-sided probability value < 0.05. All analyses were performed using Stata version 13 (Stata Corporation, College Station, TX, USA).

Data availability The datasets (Taiwan's National Health Insurance Research Database) analyzed during the current study are not publicly available due to the "Personal Information Protection Act" executed by Taiwan's government, starting from 2012 but are available from the corresponding author on reasonable request.

Results

Patient characteristics

A total of 63,786 patients were enrolled, and the HZ and non-HZ cohorts each included 31,893 patients. The baseline characteristics were significantly different between the HZ and non-HZ cohorts, including comorbidities, medication use, and socioeconomic status, except for age and sex, which were balanced by matching. Overall, there were higher proportions of comorbidities and medication use in the HZ cohort than in the non-HZ cohort (Table 1). In the HZ cohort, 28,245 patients without PHN were included in the non-PHN group, and 3648 patients with PHN were included in the PHN group. The baseline characteristics of the PHN and non-PHN groups are shown in the supplementary material (Table S1).

Risk of developing osteoporosis or any fracture

During the mean follow-up time of 6.0 years, 4639 and 5597 patients developed osteoporosis or fracture in the non-HZ and HZ cohorts, respectively. The cumulative incidence of osteoporosis or fracture was higher in the HZ cohort than in the non-HZ cohort (29.8 vs. 23.8 per 1000 person-years; log-rank test, $p < 0.001$) (Fig. 1). The Cox proportional hazard regression models revealed that HZ diagnosis was significantly associated with an elevated risk of osteoporosis or fracture in both univariate (crude HR = 1.25, 95% CI = 1.20–1.30, $p < 0.001$) and multivariate regression models (adjusted HR [aHR] = 1.20, 95% CI = 1.15–1.25, $p < 0.001$) (Table 2). In the HZ cohort, both the non-PHN and PHN groups had significantly higher risks of osteoporosis and fracture than the non-HZ cohort after adjusting for all baseline characteristics listed in Table 1, and the highest risk was found in the PHN groups (Table 2).

Table 1 Baseline characteristics of patients with and without herpes zoster

	Yes (n = 31,893)		No (n = 31,893)		p value
	n	%	n	%	
Age (years)	48.7 ± 19.1		48.7 ± 19.1		1.000
Sex					1.000
Male	16,982	53.2	16,982	53.2	
Female	14,911	46.8	14,911	46.8	
Income level (NTD)					< 0.001
Financially dependent	11,562	36.3	11,852	37.2	
1–19,999	11,879	37.2	12,497	39.2	
20,000–39,999	4933	15.5	4521	14.2	
≥ 40,000	3519	11.0	3023	9.5	
Urbanization level					0.026
1 (Most urbanized)	10,296	32.3	10,173	31.9	
2	9096	28.5	9119	28.6	
3	5523	17.3	5739	18.0	
4	4418	13.9	4216	13.2	
5 (Least urbanized)	2560	8.0	2646	8.3	
Comorbidities					
CCI score	1.56 ± 1.98		1.34 ± 1.71		< 0.001
Hypertension	6564	20.6	4826	15.1	< 0.001
DM	3080	9.7	2236	7.0	< 0.001
Coronary artery disease	2111	6.6	1387	4.3	< 0.001
Congestive heart failure	502	1.6	305	1.0	< 0.001
Hyperlipidemia	2712	8.5	1890	5.9	< 0.001
COPD	1745	5.5	1012	3.2	< 0.001
Chronic kidney disease	779	2.4	425	1.3	< 0.001
Cirrhosis	1495	4.7	1106	3.5	< 0.001
Hyperthyroidism	222	0.7	163	0.5	0.003
Hypothyroidism	105	0.3	69	0.2	0.006
Rheumatoid arthritis	190	0.6	94	0.3	< 0.001
Dementia	199	0.6	129	0.4	< 0.001
Depression	640	2.0	442	1.4	< 0.001
Parkinsonism	135	0.4	121	0.4	0.381
Epilepsy	109	0.3	109	0.3	1.000
Malignancy	1399	4.4	706	2.2	< 0.001
Use of medication					
Corticosteroids	1561	4.9	615	1.9	< 0.001
Thiazide diuretics	1799	5.6	1306	4.1	< 0.001
Loop diuretics	732	2.3	436	1.4	< 0.001
NSAIDs	6003	18.8	3422	10.7	< 0.001
Opioids	215	0.7	101	0.3	< 0.001
Statins	1972	6.2	1298	4.1	< 0.001
PPIs	805	2.5	491	1.5	< 0.001
Estrogen	359	1.1	273	0.9	0.001
Thyroxine	199	0.6	147	0.5	0.005
Antithyroid drugs	145	0.5	119	0.4	0.109
Antiepileptics	751	2.4	529	1.7	< 0.001
Antiparkinsonian	257	0.8	250	0.8	0.755
Antipsychotics	553	1.7	448	1.4	0.001
Anxiolytics	3767	11.8	2469	7.7	< 0.001
Hypnotics and sedatives	1959	6.1	1327	4.2	< 0.001
Antidepressants	1089	3.4	706	2.2	< 0.001

Continuous data are expressed as mean ± standard deviation, and categorical data are expressed as number and percentage

CCI Charlson comorbidity index, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *NTD* New Taiwan dollars, *NSAID* non-steroid antiinflammatory drug, *PPI* proton pump inhibitor

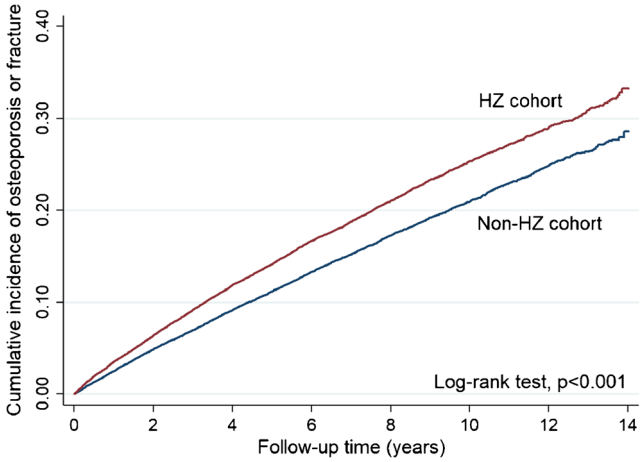

Fig. 1 Kaplan–Meier curves showing the cumulative incidence of osteoporosis or any fracture in herpes zoster (HZ) and non-HZ cohorts

Risk of developing individual events

In the analyses for each event, the HZ cohort had significant increased risks of all events, including osteoporosis (aHR = 1.32, 95% CI = 1.24–1.40, $p < 0.001$), hip fracture (aHR = 1.34, 95% CI = 1.16–1.54, $p < 0.001$), vertebral fracture (aHR = 1.38, 95% CI = 1.26–1.51, $p < 0.001$), and other fractures (aHR = 1.10, 95% CI = 1.05–1.16, $p < 0.001$), compared with the non-HZ cohort (Table 3). The cumulative incidence curve of each event is shown in Fig. 2a–d.

Similarly, in the HZ cohort, both the non-PHN and PHN groups had significantly higher risks of developing individual event, including osteoporosis, hip fracture, vertebral fracture, and other fractures, compared with those in the non-HZ cohort. Again, the highest risks of developing individual events, including osteoporosis, hip fracture, vertebral fracture, and other fractures, were observed in the PHN group (Table 3).

Analyses stratified by age and sex

After stratifying for age and sex, HZ diagnosis was significantly associated with increased osteoporosis or fracture risks in both patients with age < 65 and ≥ 65 years and in both sexes. Similarly, the highest risks of developing osteoporosis or fracture were found in patients with PHN, regardless of age or sex subgroups (Table 4).

Discussion

In this nationwide retrospective cohort study, we investigated the association between HZ and the risks of developing osteoporosis and fracture using a 15-year nationwide population database. We found that patients with HZ had higher risks of osteoporosis and fracture than those without HZ, and the risks were highest in patients with PHN. To our knowledge, this study is the first to demonstrate the association between HZ and fracture, and the only one of two large-scale studies evaluating the relationship between HZ and osteoporosis.

Previous evidence of the association between HZ and osteoporosis is limited [6–9]. One population-based observational study has previously demonstrated the association of HZ with an increased risk of osteoporosis [9]. That study concluded that the osteoporosis risk was 4.55 times higher in the patients with HZ than in those without HZ, and their results seem more significant than

Table 2 Risk of osteoporosis or fractures according to herpes zoster and postherpetic neuralgia status

	Herpes zoster cohort			Non-herpes zoster cohort
	Total	Without PHN	With PHN	
Patient numbers	31,893	28,245	3648	31,893
Events	5597	4800	797	4639
Person-years	187,814.9	168,918.7	18,896.2	195,036.1
Incidence rate[a]	29.8	28.4	42.2	23.8
Univariate model				
Crude HR (95%CI)	1.25 (1.20–1.30)	1.19 (1.15–1.24)	1.76 (1.64–1.90)	1 (ref.)
p value	< 0.001	< 0.001	< 0.001	
Multivariate model[b]				
Adjusted HR (95%CI)	1.20 (1.15–1.25)	1.17 (1.13–1.22)	1.37 (1.27–1.48)	1 (ref.)
p value	< 0.001	< 0.001	< 0.001	

[a] Per 1000 person-years

[b] Multivariate Cox proportional hazards regression model with adjustment for all baseline characteristics shown in Table 1

CI confidence interval, *HR* hazard ratio, *PHN* postherpetic neuralgia, *ref.* reference

Table 3 Risks of osteoporosis, hip fracture, vertebral fracture, and other fractures according to herpes zoster and postherpetic neuralgia status

	Events	Incidence rate[a]	Multivariate model[b]	
			Adjusted HR (95% CI)	*p* value
Osteoporosis				
Non-herpes zoster	1764	8.5	1 (ref.)	
Herpes zoster	2393	11.9	1.32 (1.24–1.40)	< 0.001
Without PHN	2025	11.2	1.30 (1.22–1.39)	< 0.001
With PHN	368	17.8	1.42 (1.27–1.59)	< 0.001
Hip fracture				
Non-herpes zoster	356	1.7	1 (ref.)	
Herpes zoster	486	2.3	1.34 (1.16–1.54)	< 0.001
Without PHN	390	2.1	1.29 (1.11–1.49)	0.001
With PHN	96	4.3	1.59 (1.26–2.00)	< 0.001
Vertebral fracture				
Non-herpes zoster	789	3.7	1 (ref.)	
Herpes zoster	1127	5.4	1.38 (1.26–1.51)	< 0.001
Without PHN	942	5.0	1.35 (1.23–1.49)	< 0.001
With PHN	185	8.4	1.53 (1.30–1.80)	< 0.001
Other fractures				
Non-herpes zoster	3033	14.9	1 (ref.)	
Herpes zoster	3408	17.1	1.10 (1.05–1.16)	< 0.001
Without PHN	2956	16.6	1.09 (1.03–1.14)	0.002
With PHN	452	21.9	1.25 (1.13–1.38)	< 0.001

[a] Per 1000 person-years

[b] Multivariate Cox proportional hazards regression model with adjustment for all baseline characteristics listed in Table 1

CI confidence interval, *HR* hazard ratio, *PHN* postherpetic neuralgia, *ref.* reference

our results. However, it should be mentioned that the previous study only included patients aged 20–49 years and excluded those aged ≥ 50 years and that the overall incidence of osteoporosis in that study was less than 1%. Current epidemiology studies have revealed that osteoporosis is mainly diagnosed in patients aged ≥ 50 years, who were excluded in that previous study, and the examination for osteoporosis was rarely performed before the age of 50 years [16–18]. Therefore, their evidence for the relationship between HZ and osteoporosis remained insufficient, and our study helps address this knowledge gap. In addition to osteoporosis, our study has also concurrently evaluated fracture risks, which have not been reported previously. We found that patients with HZ not only had significantly higher risks of osteoporosis but also had significantly higher risks of osteoporosis-related fractures (hip and vertebral fractures) and other fractures. We also observed the highest risks of osteoporosis and fracture in patients with PHN. Compared with previous studies [6–9], our study evaluated outcomes more comprehensively and with appropriate study designs.

The exact underlying mechanism of the association between HZ and osteoporosis/fracture is still not well understood, but there are some possible hypotheses. Systemic inflammation has been well recognized to have an exacerbating effect on decreasing bone mineral density and osteoporosis [19–23]. Several studies have demonstrated the association between inflammatory diseases, such as rheumatoid arthritis [24], psoriasis [25], systemic lupus erythematosus [26, 27], multiple sclerosis [28], inflammatory bowel diseases [29], ankylosing spondylitis [30], and bone loss. HZ, which involved chronic latent inflammation, can cause PHN and release inflammatory signals [9, 31]. Previous studies have elucidated that some inflammatory cytokines, such as tumor necrosis factor α and interleukins 1 and 6, are activators of osteoclastogenesis and lead to increased bone turnover and bone loss [26, 32, 33]. Previous studies have found higher levels of such inflammatory cytokines in patients with HZ, especially those with PHN [9, 34, 35]. This supported the hypothesis that sys-

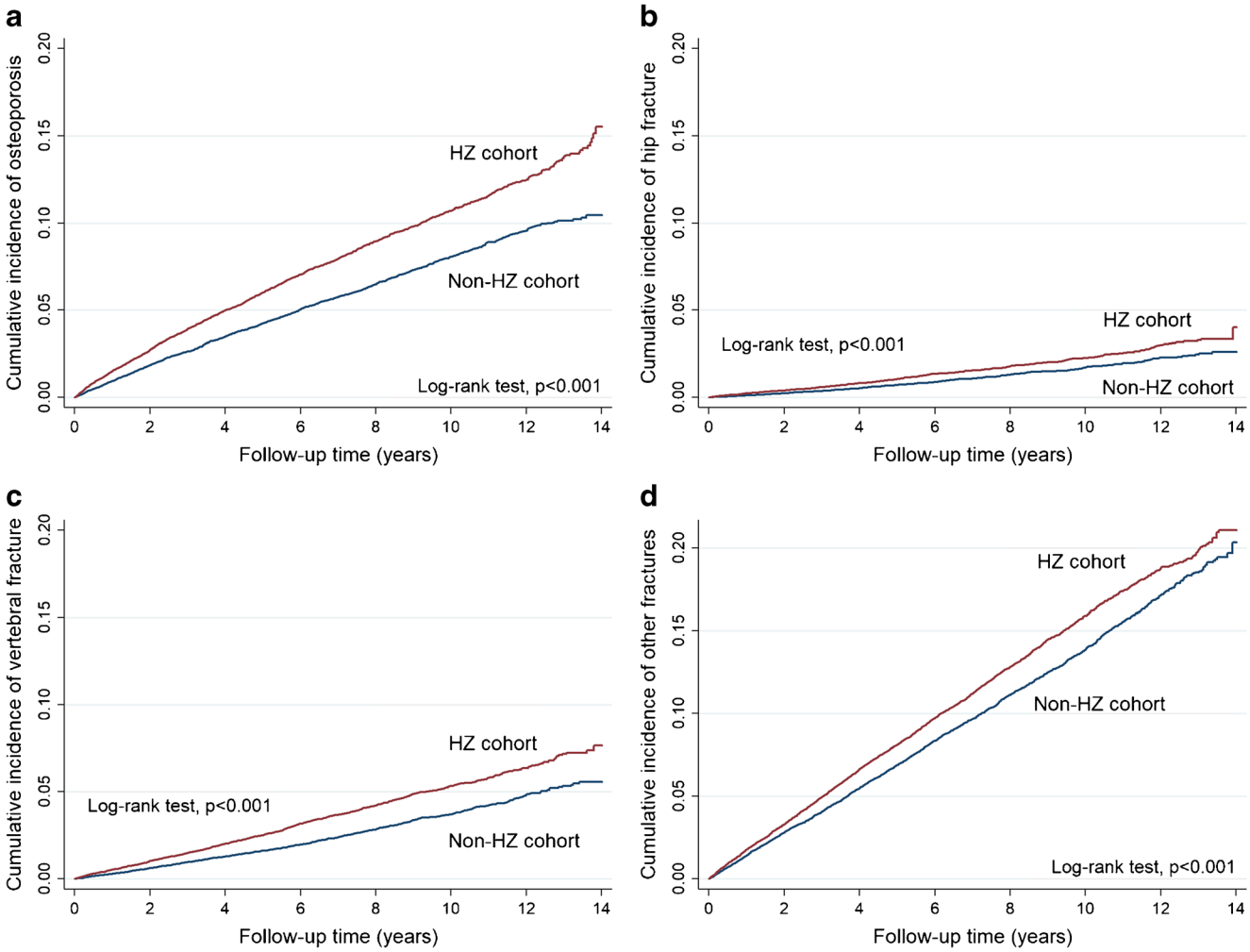

Fig. 2 Kaplan–Meier curves showing cumulative incidences of each individual event in herpes zoster (HZ) and non-HZ cohorts. **a** Osteoporosis. **b** Hip fracture. **c** Vertebral fracture. **d** Other fractures

temic inflammation may play an important role on how HZ increases the risks of osteoporosis and consequent fracture and possibly explains the findings of the highest osteoporosis and fracture risks in patients with PHN. Furthermore, medications for pain control, such as tricyclic antidepressants, gabapentin, pregabalin, and opioids, were prescribed for patients with PHN. Previous studies have suggested that antidepressants, antiepileptics, and opioids can increase the risks of osteoporosis and fracture [36–41], and this can also explain the association of such high risks found in PHN patients.

The main strength of this study is its nationwide cohort design, which provided a large sample size and a long-term follow-up time. Furthermore, this study is the first to demonstrate a clear association between HZ and fractures and one of the few studies to demonstrate an association between HZ and osteoporosis. Although the effect of HZ on osteoporosis and fracture risks was modest, the public health implications could be potentially large due to the high prevalence and incidence of HZ, osteoporosis, and fracture in the aging population worldwide.

There are limitations that should be mentioned. First, we could not retrieve some potential confounders using the claims-based dataset, such as lifestyle and psychiatric, image, or laboratory examination details (such as an individual's calcium and vitamin D status), and thus, such factors could not be controlled or adjusted for during analyses. Second, by using the claims-based dataset, we could not obtain detailed medical histories, and thus, could not determine the actual mechanism of developing fractures. Third, only de-identified patient data can be accessed owing to the patient anonymity policies of NHRI; therefore, the diagnostic accuracy cannot be confirmed directly, as when interviewing patients personally. However, the diagnostic codes for many diseases [42–46], including fractures [47], have been validated in the LHID and showed high accuracy. In addition, the National Health Insurance Bureau in Taiwan randomly and routinely reviews claims to confirm the diagnostic accuracy in every hospital, and in the case of incorrect diagnosis or coding, hospitals or doctors are heavily fined. Therefore,

Table 4 Risk of osteoporosis or fractures according to herpes zoster and postherpetic neuralgia status after stratifying age and sex

	Multivariate model[a]	
	Adjusted HR (95% CI)	*p* value
Age < 65 years		
Non-herpes zoster	1 (ref.)	
Herpes zoster	1.11 (1.06–1.17)	< 0.001
Without PHN	1.10 (1.04–1.15)	< 0.001
With PHN	1.25 (1.13–1.39)	< 0.001
Age ≥ 65 years		
Non-herpes zoster	1 (ref.)	
Herpes zoster	1.38 (1.29–1.47)	< 0.001
Without PHN	1.34 (1.25–1.44)	< 0.001
With PHN	1.58 (1.41–1.76)	< 0.001
Male		
Non-herpes zoster	1 (ref.)	
Herpes zoster	1.20 (1.13–1.27)	< 0.001
Without PHN	1.17 (1.10–1.24)	< 0.001
With PHN	1.36 (1.22–1.52)	< 0.001
Female		
Non-herpes zoster	1 (ref.)	
Herpes zoster	1.20 (1.14–1.27)	< 0.001
Without PHN	1.17 (1.11–1.24)	< 0.001
With PHN	1.40 (1.26–1.56)	< 0.001

[a] Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics listed in Table 1

CI confidence interval, *HR* hazard ratio, *PHN* postherpetic neuralgia, *ref.* reference

the validity of diagnoses and outcomes identified using data in the LHID should be acceptable.

In summary, this nationwide cohort study has identified HZ as an independent risk factor for both osteoporosis and fracture. We suggested that physicians should keep this association in mind in clinical practice for early detection of osteoporosis and prevention of fracture in patients with HZ. Further studies are needed to investigate the possible underlying mechanisms for this association and to evaluate whether the cause–effect relationship exists.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Review Board of Tzu Chi Medical Center approved this study protocol (REC No.: IRB107-60C). For this type of study, formal consent is not required.

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