

Herpes zoster as a risk factor for osteoporosis

A 15-year nationwide population-based study

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Abstract

The objective of this study was to investigate the risk of osteoporosis in patients with herpes zoster (HZ) infection using a nationwide population-based dataset. The Taiwan National Health Insurance Research Database was used to compare data between 11,088 patients aged 20 to 49 years diagnosed with HZ during 1996 to 2010 and a control group of 11,088 patients without HZ. Both cohorts were followed up until the end of 2010 to measure the incidence of osteoporosis. Cox proportional-hazards regression and Kaplan–Meier analyses were used to calculate hazard ratio and cumulative incidences of osteoporosis, respectively. The overall risk of osteoporosis was 4.55 times greater in the HZ group than in the control group (2.48 vs. 0.30 per 1000 person-years, respectively) after adjusting for age, gender, Charlson Comorbidity Index, and related comorbidities. Compared with controls, patients with HZ and subsequent postherpetic neuralgia had a 4.76-fold higher likelihood of developing osteoporosis (95% confidence interval: 2.44–9.29), which was a statistically significant difference ($P < 0.001$). Osteoporosis risk factors included female gender, age, advanced Charlson Comorbidity Index, depression, and postherpetic neuralgia. This study identified HZ is associated with an increased osteoporosis risk. Further evaluation of the value of bone mineral density test in detecting osteoporosis after HZ may be suggested. HZ vaccination could also be evaluated to lower the incidence of HZ and possibly subsequent osteoporosis. Physicians should be alerted to this association to improve early identification of osteoporosis in patients with HZ.

Abbreviations: BMD = bone mineral density, CCI = Charlson Comorbidity Index, CI = confidence interval, HR = hazard ratio, HZ = herpes zoster, IBD = inflammatory bowel diseases, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IL = interleukin, IQR = interquartile range, NHIRD = National Health Insurance Research Database, PYs = person-years, RA = rheumatoid arthritis, SD = standard deviation, SLE = systemic lupus erythematosus.

Keywords: herpes zoster, nationwide population-based study, osteoporosis

1. Introduction

Osteoporosis is a major public health problem in the elderly and in women, especially in those of Asian descent.^[1] Oden et al^[2] reported that osteoporosis could lead to nearly 50% of all hip fractures in the world. Osteoporosis-related deaths and complications can lead to increased burden on society, osteoporotic

patients, and especially their family members.^[3] As a result, to prevent osteoporosis-related fractures, disability, comorbidity, and mortality, it is rather important to ascertain risk factors and people at high risk for osteoporosis.

Herpes zoster (HZ), a latent neurotrophic viral disease caused by the varicella-zoster virus after a primary infection, is characterized by vesicular eruptions in the dermatome sometimes followed by painful neuralgia.^[4] HZ causes postherpetic neuralgia and the release of inflammatory signals.^[5] Chronic inflammation then decreases bone mass. For example, bone loss has been reported in patients with systemic lupus erythematosus (SLE), psoriasis, inflammatory bowel diseases (IBD), ankylosing spondylitis, multiple sclerosis, rheumatoid arthritis (RA), and pemphigus vulgaris.^[6–12] HZ infection and osteoporosis are also associated with several clinical conditions, including diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and depression.^[13] The relationship between osteoporosis and HZ has attracted attention since the 1950s. However, these studies have a limited scope because they involved a small sample.^[14–16] As no previous study has used population-based data to explore association between these 2 disorders, the objective of this study was therefore to examine prospectively the association between HZ and osteoporosis using a health insurance database.

2. Methods

2.1. Data sources

We used data collected from the Taiwan National Health Insurance Research Database (NHIRD) (99.9% of the 23.74 million residents of Taiwan comprised), maintained by

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the national health care system of Taiwan, to perform this population-based study. The Longitudinal Health Insurance Database 2010 compiled by the National Health Institute contains the complete medical records of 1 million randomly selected patients treated from 1996 to 2010. To code diagnoses correctly, the International Classification of Diseases, Clinical Modification, Ninth Revision (ICD-9-CM) code was used. Based on the Declaration of Helsinki, the present study was performed. Besides, the Institutional Review Board of Kaohsiung Medical University Hospital reviewed and approved the research (KMUHIRB-EXEMPT (I)-20150040).

2.2. Study population

The study cohort included 11,088 patients aged 20 to 49 years and diagnosed with HZ (ICD-9-CM code 053) during 1996 to 2010. To ensure data accuracy, the analysis was limited to patients who had received ≥ 1 diagnosis during inpatient care or ≥ 2 HZ diagnoses during ambulatory visits and who had been assigned ICD-9 codes by a dermatologist. The ICD-9-CM code was 053.19 for HZ with postherpetic neuralgia. The date of the first clinical visit for HZ was defined as the index date. The definition of the osteoporosis cases in this study was that if they received ≥ 1 diagnosis in inpatient care or ≥ 2 osteoporosis diagnoses for ambulatory visits, and the ICD-9 code was assigned by orthopedists and receiving at least 1 bone mineral density (BMD) examination.^[9,17,18] The exclusion criteria were diagnosis of osteoporosis (ICD-9-CM code 733) before and on the index date, age younger than 20 or older than 50 years, and incomplete information. A 1:1 ratio of HZ to non-HZ patients was maintained to increase statistical power and to make sure an enough number of osteoporosis group for stratified analyses. We performed a post hoc sample size calculation to determine statistical power. According to the year of HZ diagnosis and age, we used a simple random sampling method to select the non-HZ insured patients to match with each HZ patients in the same period. Thus, 11,088 cases were enrolled in the non-HZ cohort. Fig. 1 shows a flow chart of the study procedure.

2.3. Outcome and comorbidities

The patients in both the HZ and non-HZ cohorts were followed up until diagnosis with osteoporosis, withdrawal from insurance,

loss to follow-up, or the end of 2010. Baseline comorbidities identified by ICD-9-CM codes in the claims records before the index date included hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), chronic kidney disease (ICD-9-CM codes 582, 583, 585, 586, and 588), chronic liver disease (ICD-9-CM codes 456, 571, and 572), chronic obstructive pulmonary disease (ICD-9-CM code 491, 492, 494, and 496), depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), stroke (ICD-9-CM codes 430–438). The Charlson Comorbidity Index (CCI) score was used to evaluate the severity of comorbid conditions, such as diabetes, paraplegia or hemiplegia, congestive heart failure, myocardial infarction, chronic pulmonary disease, dementia, rheumatic disease, cerebrovascular disease, peripheral vascular disease, mild and moderate or severe liver disease, acquired immune deficiency syndrome, human immunodeficiency virus infection, peptic ulcer disease, renal disease, metastatic solid tumor, and any malignancy (including lymphoma and leukemia, except malignancy of skin). The CCI scores were then categorized into 4 levels: 0, 1 to 2, 3 to 4, and ≥ 5 .

2.4. Statistical analysis

In order to compare clinical characteristics and distributions of categorical demographics between the HZ and non-HZ cohorts, χ^2 test was used. The Wilcoxon rank-sum test and Student *t* test were used to compare follow-up time (*y*) and mean age between the 2 groups, as appropriately. To estimate cumulative incidence, the Kaplan–Meier method was performed. The 2-tailed log-rank test was used to calculate the differences between the curves. For HZ patients, survival was calculated until an ambulatory visit for osteoporosis, hospitalization, or the end of the study period (December 31, 2010), whichever came first. Incidence rates of osteoporosis estimated in 1000 person-years were compared between the 2 cohorts. To evaluate 95% confidence interval (CI) and hazard ratio (HR) for osteoporosis, multivariable and univariable Cox proportional hazard regression models were used. The multivariable Cox models were adjusted for gender, CCI score, age, and relevant comorbidities. Statistically significant was considered when a 2-tailed *P* value of <0.05 was calculated. We used Statistical Analysis Software, version 9.4 (SAS Institute, Cary, NC) to perform all statistical data processing and analyses.

3. Results

3.1. Baseline characteristics of patients with and without HZ

The baseline demographic characteristics and comorbidities in the 2 cohorts are compared in Table 1. In the HZ cohort, 51.94% were female. The percentages of patients with comorbidity were significantly higher in the HZ cohort compared with the non-HZ cohort for hypertension (19.85 vs. 10.08, $P < 0.001$), diabetes mellitus (11.39 vs. 5.83, $P < 0.001$), hyperlipidemia (24.95 vs. 12.79, $P < 0.001$), chronic kidney disease (6.98 vs. 3.09, $P < 0.001$), chronic liver disease (30.14 vs. 20.17, $P < 0.001$), chronic obstructive pulmonary disease (33.13 vs. 23.50, $P < 0.001$), stroke (2.08 vs. 0.91, $P < 0.001$), depression (10.38 vs. 6.81, $P < 0.001$). The HZ cohort also had higher CCI score. During a median observation time of 2.3 years, 144 (1.30%) HZ patients had osteoporosis (interquartile range [IQR]=1.1–4.4). The incidence of osteoporosis was significantly ($P < 0.001$) higher

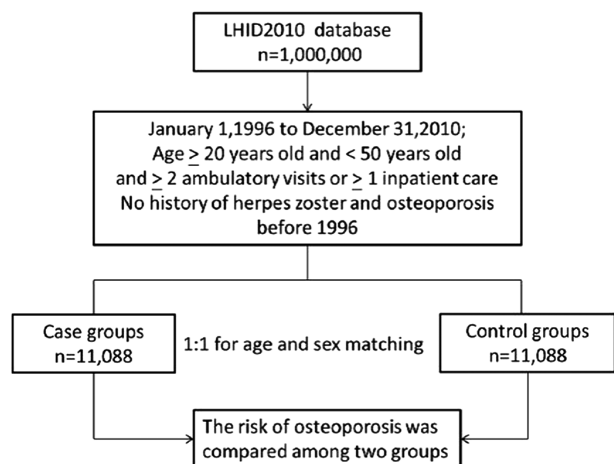


Figure 1. Flow diagram of the present study from the National Health Insurance Research Database. LHID=Longitudinal Health Insurance Database.

Table 1**Baseline characteristics of patients with and without herpes zoster infection.**

| Variables | Herpes zoster infection | | P value |
|---|-------------------------|----------------|---------|
| | Yes (N=11,088) | No (N=11,088) | |
| Osteoporosis patients, n (%) | 144 (1.30) | 50 (0.45) | <0.001 |
| Period of developing osteoporosis median (IQR), years | 2.3 (1.1–4.4) | 8.4 (4.7–11.4) | <0.001 |
| Age group, n (%) | | | |
| 20–34 | 4633 (41.78) | 4633 (41.78) | |
| 35–49 | 6455 (58.22) | 6455 (58.22) | 1.000 |
| Gender, n (%) | | | |
| Men | 5329 (48.06) | 5329 (48.06) | |
| Women | 5759 (51.94) | 5759 (51.94) | 1.000 |
| Charlson Comorbidity Index, n (%) | | | |
| 0 | 3124 (28.17) | 4920 (44.37) | |
| 1–2 | 5142 (46.37) | 4771 (43.03) | |
| 3–4 | 1884 (16.99) | 1117 (10.07) | |
| ≥5 | 938 (8.46) | 280 (2.53) | <0.001 |
| Comorbidity, n (%) | | | |
| Hypertension | 2201 (19.85) | 1118 (10.08) | <0.001 |
| Diabetes mellitus | 1263 (11.39) | 646 (5.83) | <0.001 |
| Hyperlipidemia | 2767 (24.95) | 1418 (12.79) | <0.001 |
| Chronic kidney disease | 774 (6.98) | 343 (3.09) | <0.001 |
| Chronic liver disease | 3342 (30.14) | 2236 (20.17) | <0.001 |
| Chronic obstructive pulmonary disease | 3673 (33.13) | 2606 (23.50) | <0.001 |
| Depression | 1151 (10.38) | 755 (6.81) | <0.001 |
| Stroke | 231 (2.08) | 101 (0.91) | <0.001 |

IQR=interquartile range, SD=standard deviation.

than that in the non-HZ patients (50 with osteoporosis out of 11,088 age- and gender-matched controls [0.45%]) during a median observation time of 8.4 years [IQR=4.7–11.4]. In the following periods, the osteoporosis development period was significantly shorter in the HZ group (2.3 years) compared with the non-HZ group (8.4 years).

3.2. Osteoporosis incidence and risk

The osteoporosis incidence and HRs by gender, age, and comorbidity are stratified in Table 2. During the follow-up period, 144 (1.30 %) of the HZ patients and 50 (0.45%) of the non-HZ patients developed osteoporosis. The overall

osteoporosis risk was 4.55 times greater in the HZ group compared with the non-HZ group (2.48 vs. 0.30 per 1000 person-years, respectively) after adjusting for age, gender, CCI, and related comorbidities (hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, stroke, depression). The gender-specific analyses showed that, in both cohorts, the incidence of osteoporosis was higher in women than in men (4.26 vs. 0.60 per 1000 person-years, respectively, in the HZ cohort; 0.45 vs. 0.14 per 1000 person-years, respectively, in the non-HZ cohort). Additionally, the osteoporosis risk in both sexes was significant higher (adjusted HR=4.80, 95% CI: 3.12–7.38 for women; adjusted HR=3.43, 95% CI: 1.33–8.85 for men, $P <$

Table 2**Incidence and hazard ratios of osteoporosis by demographic characteristics and comorbidity among patients with or without herpes zoster infection.**

| Variables | Patients with herpes zoster infection | | | Patients without herpes zoster infection | | | Compared with nonherpes zoster infection | |
|-----------------|---------------------------------------|----------|------|--|-----------|------|--|-----------------------------------|
| | Osteoporosis | PYs | Rate | Osteoporosis | PYs | Rate | Crude HR ^a (95% CI) | Adjusted HR ^a (95% CI) |
| Overall | 144 | 58050.06 | 2.48 | 50 | 165977.13 | 0.30 | 8.16 (5.59–11.91) ^b | 4.55 (3.09–6.72) ^b |
| Gender | | | | | | | | |
| Men | 17 | 28217.18 | 0.60 | 11 | 79873.22 | 0.14 | 5.61 (2.23–14.14) ^b | 3.43 (1.33–8.85) ^c |
| Women | 127 | 29832.87 | 4.26 | 39 | 86103.91 | 0.45 | 8.86 (5.83–13.47) ^b | 4.80 (3.12–7.38) ^b |
| Stratify by age | | | | | | | | |
| 20–34 | 14 | 23710.29 | 0.59 | 6 | 69459.68 | 0.09 | 7.73 (2.53–17.88) ^b | 4.58 (1.67–11.82) ^d |
| 35–49 | 130 | 34339.76 | 3.79 | 44 | 96517.45 | 0.46 | 8.21 (5.53–12.19) ^b | 4.44 (3.05–6.88) ^b |
| Comorbidity | | | | | | | | |
| No | 11 | 18223.39 | 0.60 | 8 | 87171.11 | 0.09 | 6.35 (2.50–16.14) ^b | 6.53 (2.56–16.62) ^b |
| Yes | 133 | 39826.67 | 3.34 | 42 | 78806.01 | 0.53 | 6.15 (4.13–9.15) ^b | 4.29 (2.86–6.45) ^b |

95% CI=95% confidence interval, HR=hazard ratio, PYs=person-years, Rate=incidence rate in per 1000 person-years.

^a Model adjusted for age, gender, Charlson Comorbidity Index and relevant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, stroke, depression).

^b $P < 0.001$.

^c $P = 0.011$.

^d $P = 0.003$.

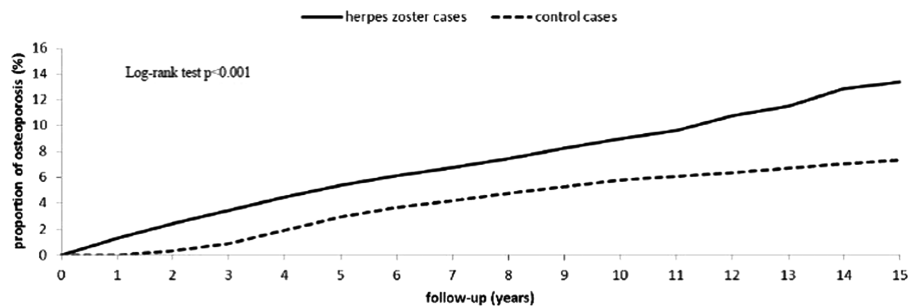


Figure 2. Cumulative incidence of osteoporosis among herpes zoster (solid line) and control (dashed line) cases.

0.001) in the HZ group than in the non-HZ group. In age-specific analysis, the incidence of osteoporosis substantially consistently increased with age in both cohorts. Compared with the non-HZ group, the HZ group had a higher osteoporosis risk in both age groups. Regardless of comorbidities, the patients with HZ exhibited a higher risk of osteoporosis than that of the non-HZ patients. The osteoporosis risk contributed by HZ had decreased by the presence of comorbidity.

The Kaplan–Meier curves for the cumulative incidence of osteoporosis between the HZ and non-HZ groups at the 15-year follow-up are compared in Fig. 2. The cumulative incidence of osteoporosis for the 2 cohorts showed that the HZ incidence curve is significant higher than that for the control cohort (log-rank test $P<0.001$).

The risks for osteoporosis of HZ and of postherpetic neuralgia are presented in Table 3. The overall osteoporosis risk was 4.55 times higher in the HZ group than in the non-HZ group. In the HZ patients, those with postherpetic neuralgia were 4.76-fold more likely to develop osteoporosis compared with those without HZ, which was statistically significant ($P<0.001$; 95% CI: 2.44–9.29).

The Cox regression analysis results are presented in Table 4, which highlighted the risk factors for osteoporosis in the HZ group: age, gender, high CCI score, and depression.

4. Discussion

To our knowledge, this study is the first population-based cohort study to assess osteoporosis risk in a population of adults with HZ. This study found that osteoporosis risk was higher in patients with HZ compared with controls. During the follow-up period, 144 (1.30 %) patients in the HZ group and 50 (0.45 %) patients in the non-HZ group developed osteoporosis. The overall osteoporosis risk was 4.55 times higher in the HZ group compared with the non-HZ group (2.48 vs. 0.30 per 1000 person-years, respectively) after adjusting for covariates. The risk of osteoporosis was even higher in those with postherpetic

neuralgia (4.76-fold). Osteoporosis risk factors after HZ infection included gender, age, a high CCI score, and depression.

Although the underlying mechanisms of the association between HZ and osteoporosis are not fully understood, clinical evidence in recent studies suggests several possible mechanisms. First, many previous studies have shown that bone mineral density (BMD) may be related to the incidence of chronic inflammatory diseases such as RA, IBD, and SLE.^[19–21] In a report of 3141 IBD patients matched with 12,564 controls enrolled from 2000 to 2010, Tsai et al^[19] showed that the IBD patients had a higher incidence of osteoporosis. Several studies also revealed that bone density loss culminating in osteoporosis is not an uncommon comorbidity in SLE. Osteoporosis occurs in 1.4% to 68% of SLE patients.^[20] Besides, Haugeberg et al^[21] found that the osteoporosis prevalence rate is approximately 2-fold higher in patients with RA compared to the controls. In the same way, many clinical conditions not mentioned above have been correlated with an increased risk of HZ and postherpetic neuralgia; these include chronic conditions such as diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and depression.^[13] Since both HZ and osteoporosis are strongly correlated with many common risk factors, we thought that HZ is highly associated with osteoporosis.

Another pathogenic process that has well-known exacerbating effects on osteoporosis is inflammation. HZ causes postherpetic neuralgia and release inflammatory signals. Zhu et al reported significantly higher levels of interleukin (IL)-1b, IL-6, tumor necrosis factor- α , IL-8, and IL-10 in patients with HZ compared with healthy controls. Furthermore, the HZ patients, especially those with postherpetic neuralgia, had significantly higher serum concentrations of IL-6 compared with controls.^[5] IL-6 is a potent stimulator of osteoclast-induced bone resorption and central to the pathogenesis of bone loss in the context of chronic inflammation.^[22] Chronic inflammation on the endothelium cells of vascular walls may lead to damaging the common pathophysiological mechanisms of the bone and vasculature and cause osteoporosis. Therefore, the potential for osteoporosis is

Table 3

Incidence rates and hazard ratios of osteoporosis risk in patients of herpes zoster infection and of post herpetic neuralgia.

| Variables | N | Osteoporosis | PYs | Rate | Crude HR ^a (95% CI) | Adjusted HR ^a (95% CI) |
|---------------------------------|-------|--------------|-----------|------|--------------------------------|-----------------------------------|
| Without herpes zoster infection | 11088 | 50 | 165977.13 | 0.30 | Ref | Ref |
| Herpes zoster infection | 11088 | 144 | 58050.06 | 2.48 | 8.16 (5.59–11.91) ^b | 4.55 (3.09–6.72) ^b |
| Postherpetic neuralgia | 850 | 12 | 4465.62 | 2.69 | 8.45 (4.57–17.12) ^b | 4.76 (2.44–9.29) ^b |

95% CI=95% confidence interval, HR=hazard ratio, PYs=person-years, Rate=incidence rate in per 1000 person-years.

^a Model adjusted for age, gender, Charlson Comorbidity Index and relevant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, stroke, depression).

^b $P<0.001$.

Table 4**Cox regression model: significant predictors of osteoporosis after herpes zoster infection.**

| Variables | Adjusted HR ^a | (95% CI) | P value |
|----------------------------|--------------------------|-------------|---------|
| Age | 1.56 | (1.37–1.77) | <0.001 |
| Gender | 3.22 | (1.49–5.79) | <0.001 |
| Charlson Comorbidity Index | 1.58 | (1.32–1.89) | <0.001 |
| Depression | 1.84 | (1.34–2.54) | <0.001 |

95% CI = 95% confidence interval, HR = hazard ratio.

^aThe adjusted HR and 95% CI were estimated by a stepwise the Cox proportional hazards regression method.

increased by HZ with postherpetic neuralgia via IL-6 and other cytokines.

The strength of our study lies in the use of a population-based dataset for a large number of patients. Although this study identified an association between HZ and osteoporosis risk, several limitations must be considered when interpreting these results. First, HZ patients could only be identified by ICD-9 codes, the main purpose of which is administrative billing, and serology data were unavailable for use in clinical validation. However, diagnostic accuracy was enhanced by limiting the study population to patients who had received medical care for osteoporosis on ≥ 2 separate visits. Furthermore, the many medical experts from the Professional Peer Review Committee at the Bureau of National Health Insurance conduct regular scrutiny to check the accuracy of diagnostic codes used in health insurance claims. Hospitals and doctors are subject to big penalties for incorrect entries of diagnostic codes. Finally, the diagnoses and codes for HZ used in our study should be as reliable as previous studies.^[23–25] Second, some patients in Taiwan are highly superstitious and attempt to eliminate HZ through various religious ceremonies or folk remedies instead of seeking medical attention. Therefore, this study may have underestimated the actual incidence of HZ. Another limitation of this study is the use of a claims database containing no personal data such as exercise capacity, body mass index, imaging results, nutritional supplements, disease severity, and biochemistry profiles, which potentially affects our reports. Additionally, although we adjusted for several potential confounders, the database did not include smoking, alcohol use, and other variables that might be associated with HZ.^[26] Third, most Taiwan residents are Chinese descent; further studies are needed to see whether our findings are applicable in other races. Last but not least, as in all population-based studies, statistical significance cannot always be equated with clinical significance.

In summary, this study identified that HZ is an independent risk factor for osteoporosis, HZ may be a prodromal warning sign of osteoporosis. Therefore, the value of BMD tests should be considered in patients diagnosed with HZ and HZ vaccination could be evaluated to lower the incidence of HZ and subsequent osteoporosis. Physicians should be alerted to this association to improve early identification of osteoporosis in patients with HZ.

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