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Real-world database investigating the association between diabetes mellitus and herpes zoster in Taiwan

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Abstract
Little evidence is available about the correlation between diabetes mellitus and herpes zoster in Taiwan. This study aimed to investigate the correlation between diabetes mellitus and herpes zoster in Taiwan.

A population-based cohort study was conducted using the database of Taiwan National Health Insurance Program. There were 27,369 subjects aged 20 to 84 years with newly diagnosed diabetes mellitus from 2000 to 2012 as the diabetes mellitus group and 107,705 sex- and age-matched subjects without diabetes mellitus as the nondiabetes mellitus group. The incidence of herpes zoster at the end of 2013 was estimated. The multivariable Cox proportional hazards regression model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) of herpes zoster associated with diabetes mellitus.

The overall incidence of herpes zoster was 1.16-fold higher in the diabetes mellitus group than the nondiabetes mellitus group (7.85 vs 6.75 per 1000 person-years, 95% CI 1.12–1.20). After adjustment for co-variables, the adjusted HR of herpes zoster was 1.17 for subjects with diabetes mellitus (95% CI 1.10–1.23), compared with subjects without diabetes mellitus.

Patients with diabetes mellitus are associated with 1.17-fold increased risk for developing herpes zoster.

Abbreviation: ICD-9 code = International Classification of Diseases, Ninth Revision, Clinical Modification.

Keywords: cohort study, diabetes mellitus, herpes zoster, Taiwan National Health Insurance Program

1. Introduction

In 2016, there were approximately 2082,8000 new cases of diabetes mellitus and 383,453,000 cases with diabetes mellitus in

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the world.[1] In 2017, diabetes mellitus and its complications were the fifth leading cause of death in Taiwan.[2] There were 9845 deaths related to diabetes mellitus, which accounted for 5.73% of 171,857 total deaths in Taiwan in 2017.[2] In addition to its microvascular and macrovascular complications, diabetes mellitus has been found to be associated with immunologic dysfunctions,[3,4] which have let diabetic patients more susceptible to developing infections, including lower respiratory tract infection, pulmonary tuberculosis, pleural empyema, urinary tract infection, and skin infection.[5–7]

Herpes zoster is caused by the reactivation of latent varicella-zoster virus in sensory ganglia when an individual's specific cell-mediated immunity to varicella-zoster virus is waning, which is caused by the underlying etiologies.[8,9] Based on the theory of decreased specific cell-mediated immunity to varicella-zoster virus found in diabetic patients,[10] previous epidemiological studies have demonstrated that diabetic patients have an increased risk for development of herpes zoster,[11–14] but little evidence is available about the correlation between diabetes mellitus and herpes zoster in Taiwan.

Given diabetes mellitus being a public health concern in Taiwan due to its high prevalence, incidence, and mortality,[2,15] a population-based cohort study was conducted using the database of the Taiwan National Health Insurance Program to investigate the correlation between diabetes mellitus and herpes zoster in Taiwan.

2. Methods

2.1. Study design and data source

A population-based cohort study was conducted using the database of Taiwan National Health Insurance Program. The program was launched in March 1, 1995, and it has covered

about 99.6% of 23 million residents living in the independent country of Taiwan.[16,17] The database of Taiwan National Health Insurance Program contains reimbursement claim data of each insured individual, including sex, birth date, and all medical service records. The details of the program can be found in previous studies.[18–20]

2.2. Study subjects

Subjects aged 20 to 84 years with newly diagnosed diabetes mellitus from 2000 to 2012 were selected as the diabetes mellitus group (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9 code 250). The date for diagnosing diabetes mellitus was defined as the index date. For every subject with diabetes mellitus, nearly 4 subjects without diabetes mellitus were selected from the same database as the nondiabetes mellitus group. The diabetes mellitus and the nondiabetes mellitus groups were matched for sex, age (in 5-year span), comorbidities, and the year of index date (Fig. 1).

2.3. Major outcome

The main outcome was a new diagnosis of herpes zoster during the follow-up period. Each subject was followed from the index date until the subject being diagnosed with herpes zoster, or until the end of 2013.

2.4. Comorbidities

Comorbidities before the index date were included as follows: alcohol-related disease, cancer, chronic kidney disease, chronic liver disease including cirrhosis, hepatitis B, hepatitis C, and other chronic hepatitis, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, as well as cardiovascular disease including coronary artery disease, heart failure, cerebrovascular disease, and peripheral atherosclerosis. All comorbidities were diagnosed based on ICD-9 codes, which have been well assessed in previous studies.[21–24]

2.5. Statistical analysis

The distributions of sex, age, and comorbidities between the diabetes mellitus group and the nondiabetes mellitus group were analyzed by using the Chi-square test for categorical variables and the t test for continuous variables. The incidence of herpes zoster was estimated as the event number of herpes zoster found during the follow-up period, divided by the total follow-up person-years for each group. The incidence rate ratio with 95% confidence interval (CI) of herpes zoster for diabetes mellitus group versus non-diabetes mellitus group was estimated by using Poisson regression, stratified by sex and age. All variables were included in a univariable model. Those variables found to be statistically significant in a univariable model were further included in a multivariable model. The multivariable Cox
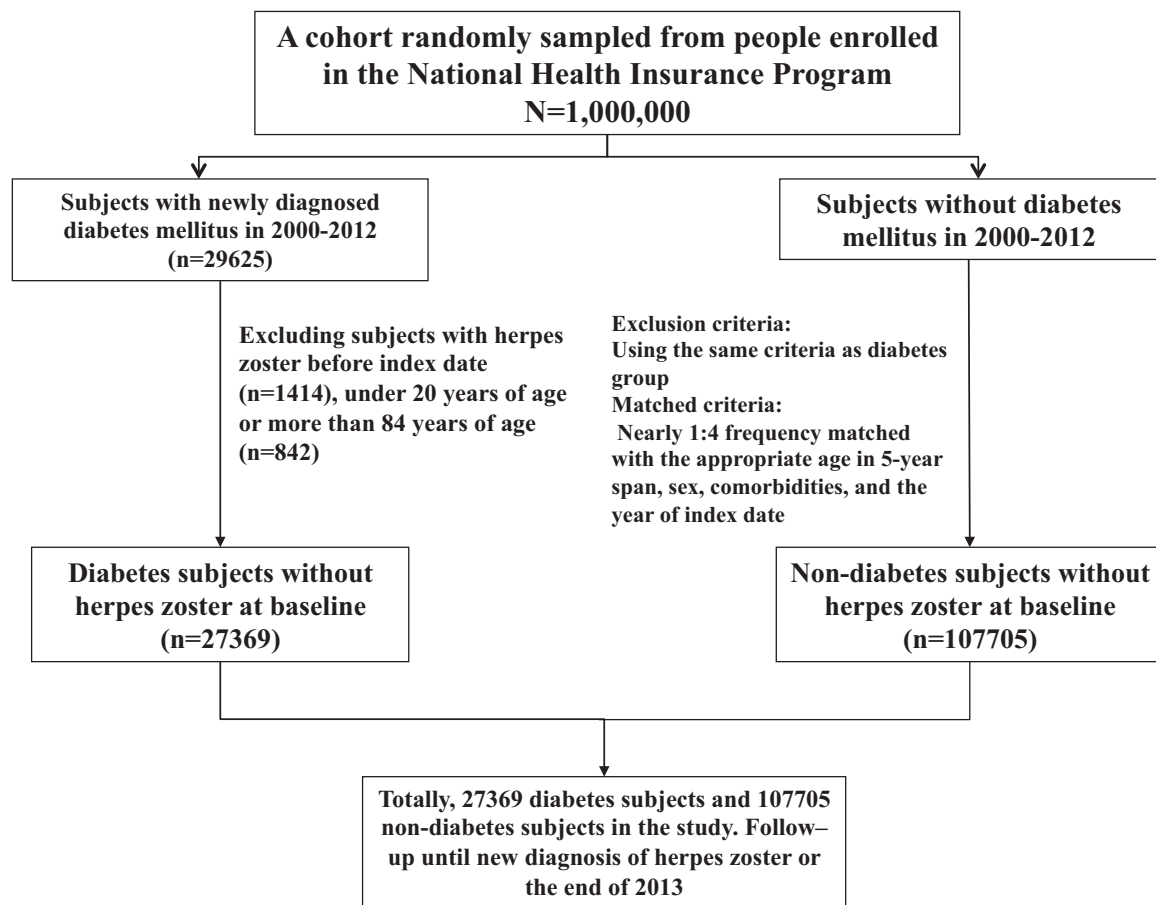

Figure 1. Flowchart of study subjects' selection.

Table 1

Baseline information between diabetes mellitus group and nondiabetes mellitus group.

Variable	Nondiabetes N = 107705		Diabetes mellitus N = 27369		P-value*
	n	(%)	n	(%)	
Sex					.98
Female	48063	(44.6)	12211	(44.6)	
Male	59642	(55.4)	15158	(55.4)	
Age group, yr					.78
20–39	28056	(26.1)	7122	(26.0)	
40–64	43925	(40.8)	11111	(40.6)	
65-84	35724	(33.2)	9136	(33.4)	
Age, yr, mean ± standard deviation†	58.1 ± 12.9		58.5 ± 12.7		<0.001
Baseline comorbidities					
Alcohol-related disease	5479	(5.09)	1575	(5.75)	.001
Cancer	2817	(2.62)	857	(3.13)	.001
Cardiovascular disease	39724	(36.9)	10180	(37.2)	.34
Chronic kidney disease	5271	(4.89)	1504	(5.50)	.001
Chronic liver disease	22173	(20.6)	5817	(21.3)	.02
Chronic obstructive pulmonary disease	20940	(19.4)	5442	(19.9)	.10
Hyperlipidemia	45678	(42.4)	11717	(42.8)	.23
Hypertension	66009	(61.3)	16821	(61.5)	.60

Data are presented as the number of subjects in each group, with percentages given in parentheses.
* Chi-square test, and
† t test comparing subjects with and without diabetes mellitus.

proportional hazards regression model was used to calculate the hazard ratio (HR) and 95% CI of herpes zoster associated with diabetes mellitus and comorbidities. All statistical analyses were performed by using the SAS 9.2 version (SAS Institute, Cary, NC). Two-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study population

Table 1 disclosed the distributions of sex, age, and comorbidities between the diabetes mellitus group and the nondiabetes mellitus group. There were 27,369 subjects with diabetes mellitus and 107,705 subjects without diabetes mellitus, with a similar distribution of sex. Males constituted a higher proportion of the study population (55.4%). The mean ages (standard deviation) of the study subjects were 58.5 (12.7) years in the diabetes mellitus group and 58.1 (12.9) years in the nondiabetes mellitus group (t test, $P < .001$). The proportions of alcohol-

related disease, cancer, chronic kidney disease, and chronic liver disease were significantly higher in the diabetes mellitus group than the non-diabetes mellitus group (Chi-square test, $P < .05$).

3.2. Incidences of herpes zoster stratified by sex and age

Table 2 disclosed the incidences of herpes zoster stratified by sex and age. At the end of the cohort study, the overall incidence of herpes zoster was 1.16-fold higher in the diabetes mellitus group than the nondiabetes mellitus group (7.85 vs 6.75 per 1000 person-years, 95% CI 1.12–1.20). The incidences of herpes zoster, as stratified by sex and age, were all higher in the diabetes mellitus group than the non-diabetes mellitus group. The diabetes mellitus group aged 65 to 84 years had the highest incidence of herpes zoster (10.5 per 1000 person-years). During the first 3 years of follow-up, the incidence of herpes zoster was 1.29-fold higher in the diabetes mellitus group than that in the nondiabetes mellitus group (7.38 vs 5.73 per 1000 person-years, 95% CI 1.24–1.34). After 3 years of follow-up, the incidence of herpes

Table 2

Incidences of herpes zoster stratified by sex and age between diabetes mellitus group and nondiabetes group.

Variable	Nondiabetes				Diabetes mellitus				IRR†	(95% CI)
	N	Event	Person-yr	Incidence*	N	Event	Person-yr	Incidence*		
All	107705	6057	897807	6.75	27369	1676	213530	7.85	1.16	(1.12,1.20)
Sex										
Female	48063	3113	419439	7.42	12211	853	99802	8.55	1.15	(1.09, 1.21)
Male	59642	2944	478368	6.15	15158	823	113728	7.24	1.18	(1.12, 1.23)
Age group, yr										
20–39	28056	768	244204	3.14	7122	248	58914	4.21	1.34	(1.25, 1.44)
40–64	43925	2656	379585	7.00	11111	759	90607	8.38	1.20	(1.14, 1.26)
65-84	35724	2633	274017	9.61	9136	669	64010	10.5	1.09	(1.02, 1.15)

CI = confidence interval, IRR = incidence rate ratio.
* Incidence: per 1000 person-years.
† IRR (incidence rate ratio): diabetes mellitus versus nondiabetes (95% confidence interval)
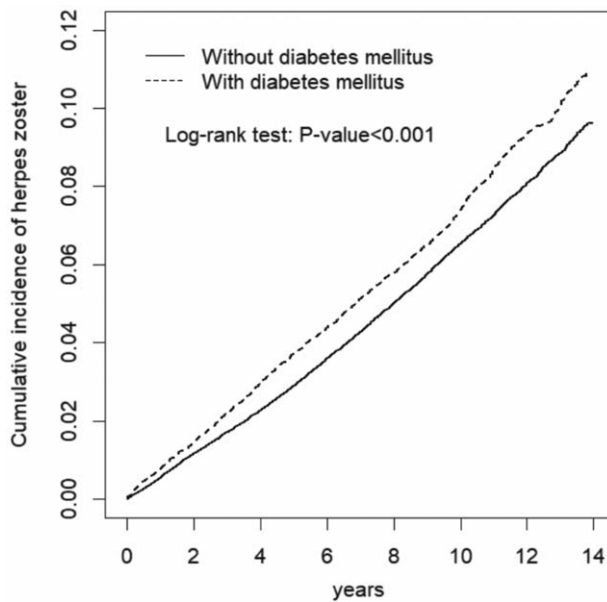
Figure 2. The Kaplan–Meier model disclosed that the diabetes mellitus group had a higher cumulative incidence of herpes zoster than the non-diabetes group at the end of follow-up (*P* < .001).

zoster was 1.12-fold higher in the diabetes mellitus group than the nondiabetes mellitus group (8.11 vs 7.27 per 1000 person-years, 95% CI 1.07–1.16).

The Kaplan–Meier model disclosed that the diabetes mellitus group had a higher cumulative incidence of herpes zoster than the nondiabetes mellitus group at the end of follow-up (9.36% vs 8.08%, *P* < .001, Fig. 2).

3.3. HR of herpes zoster associated with diabetes mellitus and comorbidities

After adjustment for co-variables, the adjusted HR of herpes zoster was 1.17 for subjects with diabetes mellitus (95% CI 1.10–1.23), compared with subjects without diabetes mellitus (Table 3). In addition, female (adjusted HR 1.07, 95% CI 1.03–1.12), age

(every 1 year, adjusted HR 1.03, 95% CI 1.03–1.03), cancer (adjusted HR 1.23, 95% CI 1.06–1.41), cardiovascular disease (adjusted HR 1.05, 95% CI 1.00–1.11), chronic obstructive pulmonary disease (adjusted HR 1.21, 95% CI 1.15–1.28), and hyperlipidemia (adjusted HR 1.15, 95% CI 1.10–1.20), were statistically associated with herpes zoster.

In further analysis in subjects with diabetes mellitus, the adjusted HR of herpes zoster was 0.31 for subjects with use of any antidiabetic drugs (95% CI 0.25–0.38, Table not shown), compared with no use of antidiabetic drugs.

4. Discussion

Although not showing the new knowledge, we observed that the incidence of herpes zoster was higher in patients with diabetes mellitus than patients without diabetes mellitus (7.85 vs 6.75 per 1000 person-years), even after 3 years of follow-up. The incidence of herpes zoster in diabetic patients in Taiwan seemed to be lower than those in Spain and in USA (7.85, 9.3, and 7.96 per 1000 person-years, respectively).[12,13] We observed that the diabetes mellitus group had a higher cumulative incidence of herpes zoster than the nondiabetes mellitus group at the end of follow-up shown by the Kaplan–Meier model. Based on the above findings, we highlight that the risk of herpes zoster remains to be high over time in diabetic patients, even after 3 years of follow-up.

After adjustment for co-variables, we observed that diabetic patients were associated with a 1.17-fold increased risk of herpes zoster, which was compatible with previous epidemiological studies.[11–14] Because the live herpes zoster vaccine effectively increases specific cell-mediated immunity to varicella-zoster virus,[25] from a point of primary prevention, we suggest diabetic patients should receive the live herpes zoster vaccine, particularly for older adults with diabetes mellitus due to their higher incidence of herpes zoster (10.5 per 1000 person-years, Table 2).

As well known, the hemoglobin A1c levels indicate the status of glycemic control. One cohort study in Denmark disclosed that patients with high hemoglobin A1c levels were at increased risk of infections.[26] This could partially explain our findings that patients taking any antidiabetic drugs were associated with a reduced risk of herpes zoster (adjusted HR 0.31), compared with

Table 3

Hazard ratio and 95% confidence interval of herpes zoster associated with diabetes mellitus and comorbidities.

Variable	Crude		Adjusted[*]	
	HR	(95% CI)	HR	(95% CI)
Sex (female vs male)	1.19	(1.14, 1.24)	1.07	(1.03, 1.12)
Age (every 1 year)	1.03	(1.03, 1.03)	1.03	(1.03, 1.03)
Diabetes mellitus (yes vs no)	1.17	(1.11, 1.24)	1.17	(1.10, 1.23)
Baseline comorbidities (yes vs no)				
Alcohol-related disease	0.82	(0.72, 0.93)	1.04	(0.91, 1.19)
Cancer	1.38	(1.19, 1.59)	1.23	(1.06, 1.41)
Cardiovascular disease	1.41	(1.35, 1.47)	1.05	(1.00, 1.11)
Chronic kidney disease	1.31	(1.19, 1.45)	1.09	(0.99, 1.21)
Chronic liver disease	1.05	(0.99, 1.11)	–	–
Chronic obstructive pulmonary disease	1.50	(1.43, 1.58)	1.21	(1.15, 1.28)
Hyperlipidemia	1.22	(1.17, 1.27)	1.15	(1.10, 1.20)
Hypertension	1.43	(1.37, 1.50)	1.04	(0.99, 1.10)

CI = confidence interval, HR = hazard ratio.

[*] Variables found to be statistically significant in the univariable model were further included in the multivariable model. Adjusted for sex, age, alcohol-related disease, cancer, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, and hypertension

those not taking antidiabetic drugs. That is, patients taking antidiabetic drugs could have low hemoglobin A1c levels. Thus, the risk of infections including herpes zoster further reduced. Moreover, due to the natural limitation of the database, the hemoglobin A1c levels were not obtained in the database. We were unable to confirm whether an optimal glycemic control could reduce the development of herpes zoster. It indicates a future research direction on the correlation between the hemoglobin A1c levels and herpes zoster.

We conclude that patients with diabetes mellitus are at increased risk for developing herpes zoster. Vaccination of herpes zoster should be suggested among patients with diabetes mellitus.

Author contributions

Specific author contributions: Shih-Wei Lai contributed to the conception of the article, initiated the draft of the article, and has approved the final draft submitted.

Conceptualization: Shih-Wei Lai.
Formal analysis: Cheng-Li Lin, Kuan-Fu Liao.
Writing – original draft: Shih-Wei Lai.
Writing – review and editing: Shih-Wei Lai.

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