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ORIGINAL ARTICLE

Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections—a Nationwide, Population-Based Cohort Study in Taiwan

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Abstract

This retrospective cohort study is to investigate the association between herpes simplex virus (HSV) infections and dementia, and the effects of anti-herpetic medications on the risk involved, using Taiwan's National Health Insurance Research Database (NHIRD). We enrolled a total of 33,448 subjects, and identified 8362 with newly diagnosed HSV infections and 25,086 randomly selected sex- and age-matched controls without HSV infections in a ratio of 1:3, selected from January 1, to December 31, 2000. A multivariable Cox proportional hazards regression model was used to evaluate the risk of developing dementia in the HSV cohort. This analysis revealed an adjusted hazard ratio of 2.564 (95% CI: 2.351-2.795, $P < 0.001$) for the development of dementia in the HSV-infected cohort relative to the non-HSV cohort. Thus, patients with HSV infections may have a 2.56-fold increased risk of developing dementia. A risk reduction of dementia development in patients affected by HSV infections was found upon treatment with anti-herpetic medications (adjusted HR = 0.092 [95% CI 0.079-0.108], $P < 0.001$). The usage of anti-herpetic medications in the treatment of HSV infections was associated with a decreased risk of dementia. These findings could be a signal to clinicians caring for patients with HSV infections. Further research is, therefore, necessary to explore the underlying mechanism(s) of these associations.

Key Words Herpes simplex virus · Dementia · National Health Insurance Research Database · Anti-herpetic medications · Cohort study

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Introduction

Dementia is one of the major global health problems. In Taiwan, the prevalence is up to 8% among those aged ≧ 65 in community studies [1, 2]. There are 35.6 million people worldwide who have dementia, with 7.7 million new cases being diagnosed each year, and the incidence continues to rise with the aging population [3]. It is, therefore, considered a heavy burden to family members, caregivers, and society [4–6].

Herpes simplex virus (HSV) infections in non-genital or genital regions are considered as common viral blister diseases [7, 8]. In previous studies, HSV infections have also been reported to be related to Alzheimer dementia [9–11]. Nonetheless, a nationwide, population-based, matched cohort study is still needed to clarify the association between HSV infections and dementia. Furthermore, we have also carried out this study to investigate whether treatment with anti-herpetic medications could attenuate the risk of developing dementia in patients with HSV infections.

Methods

Data Sources and Ethics

The National Health Insurance (NHI) Program was launched in Taiwan in 1995, and as of June 2009, it included contracts with 97% of the medical providers with approximately 23 million beneficiaries, or more than 99% of the entire population [12]. The NHIRD includes comprehensive data on inpatient care, ambulatory care, dental care, and prescription drugs availed by the insured as well as their sex and date of birth. Pursuant to the Personal Information Protection Act, individual identifiers are encrypted before release for research. The diagnoses recorded in the NHIRD are coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). All diagnoses of dementia were made by board-certified psychiatrists or neurologists, and HSV infections were confirmed by dermatologists or infection specialists according to the clinical, laboratory, and imaging findings. In Taiwan, the diagnosis, differential diagnosis from herpes zoster, and typing of HSV was based on the results of serum examinations including ELISA, antibody test or PCR in each individual case. The identification of HSV infection using insurance claims dataset was valid and has been used in previous studies [13–15]. Licensed medical records technicians verified the coding before claiming the reimbursements in hospitals and clinics. The NHI Bureau appoints several senior external specialists in neurology, psychiatry, dermatology or infection medicine for randomly reviewing the records of ambulatory care visits and inpatient claims to verify the accuracy of the diagnoses [16]. In this study, we used data from the NHIRD to investigate the association between subjects with HSV infections and dementia over a 10-year period, from the total outpatient and inpatient Longitudinal Health Insurance Database (LHID) in Taiwan (2000-2010). This study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGH IRB No. 1-104-05-145). Because the patient identifiers were encrypted before their data were used for research purposes to protect confidentiality, the requirement for written or verbal consent from patients for data linkage was waived.

Study Design and Sampled Participants

This study used a matched cohort design. From the LHID, we identified the 8362 subjects as being ≧ 50 years old with newly diagnosed HSV infections, that were selected from January 1, to December 31, 2000, according to ICD-9-CM codes 054: including genital HSV (ICD-9-CM 054.1, HSV-2) and non-genital HSV (ICD-9-CM 054.xx other than 054.1, HSV-1) infections. Each enrolled HSV patient was required to have made at least three outpatient visits within the one-year study period for symptomatic HSV infections according to these ICD-9-CM codes. The date of the HSV infection diagnosis was defined as the index date. For each patient with HSV infection, three controls without a history of HSV infections, which were frequency-matched for the exact age, sex, and index year in the control group ($N = 25{,}086$), were enrolled in this study. In addition, patients diagnosed with dementia or HSV infections before 2000 or before the first visit for HSV infections, and all patients aged < 50 were excluded. Data on the usage of anti-herpetic medications, such as acyclovir, famciclovir, ganciclovir, idoxuridine, penciclovir, tromantadine, valaciclovir, and valganciclovir, were collected.

The data of the defined daily dose (DDD) were obtained from the WHO Collaborating Centre for Drug Statistics Methodology (https://www.whocc. no/), and the duration of the usage of anti-herpetic medications was calculated by dividing the cumulative doses by the DDD of the anti-herpetic medications.

While we analyzed the effects on the risk of dementia between the two subgroups with or without anti-herpetic treatment, the sample was divided by the covariates with reference to previous studies using the NHIRD, about the treatment effects of medication associated with the risk of dementia [17–19].

Covariates

The covariates included sex, age group (50-64, ≥ 65 years), geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence (levels 1 to 4), levels of hospitals as medical centers, regional and local hospitals, and monthly income (in New Taiwan Dollars [NT$]; < 18,000, 18,000-34,999, ≥ 35,000). The urbanization level of

Table 1 Characteristics of study subjects at baseline

HSV infections	Total $n = 33,448$		With $n = 8362$		Without $n = 25,086$		P
Characteristics	n	%	n	%	n	%	
Gender							0.999
Male	18,896	56.49	4724	56.49	14,172	56.49	
Female	14,552	43.51	3638	43.51	10,914	43.51	
Age group (years)							0.999
50-64	10,292	30.77	2573	30.77	7719	30.77	
≧ 65	23,156	69.23	5789	69.23	17,367	69.23	
Catastrophic illness card							< 0.001***
Without	28,517	85.26	6307	75.42	22,210	88.54	
With	4931	14.74	2055	24.58	2876	11.46	
Insured premium (NT$)							0.088
< 18,000	33,079	98.90	8267	98.86	24,812	98.91	
18,000-34,999	335	1.00	81	0.97	254	1.01	
≧ 35,000	34	0.10	14	0.17	20	0.08	
CCI_R	1.30 ± 2.20		1.47 ± 2.36		1.25 ± 2.13		< 0.001***
Urbanization level							< 0.001***
1 (The highest)	11,082	33.13	3062	36.62	8020	31.97	
2	15,057	45.02	3809	45.55	11,248	44.84	
3	2169	6.48	381	4.56	1788	7.13	
4 (The lowest)	5140	15.37	1110	13.27	4030	16.06	
Location							< 0.001***
Northern Taiwan	13,536	40.47	3739	44.71	9797	39.05	
Middle Taiwan	8999	26.90	1955	23.38	7044	28.08	
Southern Taiwan	8545	25.55	2028	24.25	6517	25.98	
Eastern Taiwan	2198	6.57	615	7.35	1583	6.31	
Outlets islands	170	0.51	25	0.30	145	0.58	

P: chi-square/Fisher exact test (at category variable), or *t* test (at continue variable)

CCI_R = Charlson comorbidity index removed dementia

*$P < 0.05$ for comparison between patients with or without HSV infections

**$P < 0.01$ for comparison between patients with or without HSV infections

***$P < 0.001$ for comparison between patients with or without HSV infections

residence was defined according to the population, along with various indicators of the level of political, economic, cultural, and metropolitan development. Level 1 was defined as a population of > 1,250,000, and a specific designation as political, economic, cultural, and metropolitan development. Level 2 was defined as a population between 500,000 and 1,249,999, and as playing an important role in the political system, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149,999 and 499,999, and < 149,999, respectively [20].

The Charlson comorbidity index (CCI) is the most widely used comorbidity index [21, 22]. There are 22 conditions in the CCI [23], and three of these conditions are risk factors for AD: diabetes, cerebrovascular disease, and hemiplegia (stroke) [24]. Comorbidities were assessed using the CCI, which categorizes comorbidities using the ICD-9-CM codes, scores each comorbidity category, and combines all scores to calculate a single comorbidity score. A score of zero indicates that no comorbidities were found, and higher scores indicate higher comorbidity burdens [25].

Study Outcomes

All study participants were followed from the index date until the onset of dementia (ICD-9-CM codes: 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.41, 290.42, 290.43, 290.8, 290.9, and 331.0), withdrawal from the NHI program, or the end of 2010. These patients with dementia were grouped as Alzheimer dementia (AD, ICD-9-CM 331.0), vascular dementia (VaD, ICD-9-CM 290.41-290.43), and other dementia (ICD-9-CM 290.0, 290.10-290.13, 290.20-290.21, 290.3, 290.8-290.9).

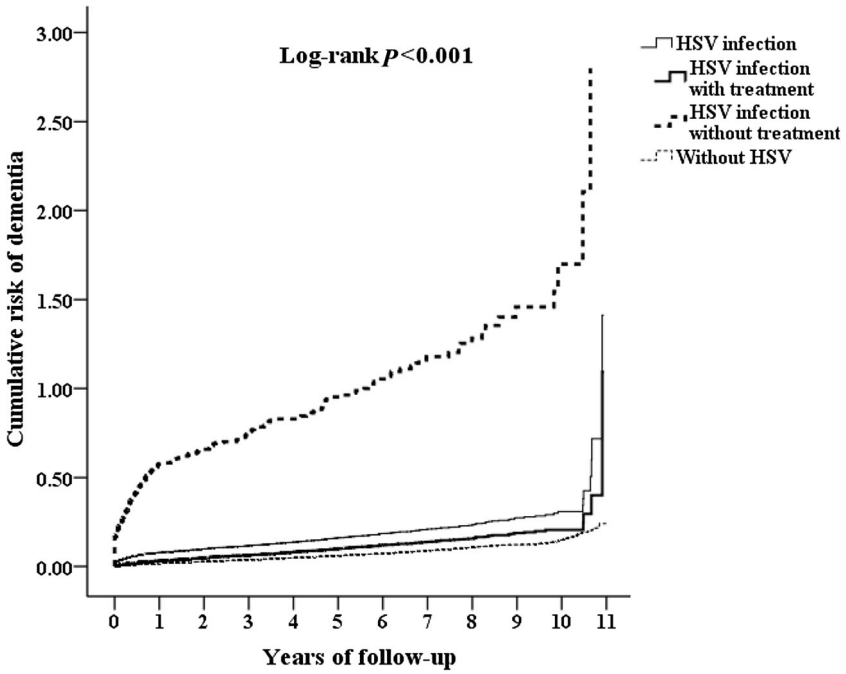

Fig. 1 Cumulative risk of dementia among subjects aged 50 and over stratified by HSV infections among three groups of controls, HSV infection with anti-herpetic treatment and HSV infection without anti-herpetic treatment in the same plot with log-rank test

Statistical Analysis

All analyses were performed using the SPSS software version 22 (SPSS Inc., Chicago, Illinois, USA). χ^2 and t tests were used to evaluate the distribution of the categorical and continuous variables, respectively. The Fisher exact test for categorical variables was used to statistically examine the differences between the two cohorts. The multivariate Cox proportional hazards regression analysis was used to determine the risk of dementia, and the results were presented as a hazard ratio (HR) with a 95% confidence interval (CI). The difference in the risk of dementia, between HSV-infected subjects and control groups was estimated using the Kaplan-Meier method with the log-rank test. A 2-tailed P value < 0.05 was considered to indicate the statistical significance.

Results

Table 1 shows the sex, age, comorbidities, urbanization, area of residence, income of the HSV patients, and the controls. When compared to controls, HSV patients tended to have higher CCI scores. HSV patients tended to have higher rates in living in urbanization level 1 or 2 areas, and in the north and east of Taiwan, than the control groups. The cumulative incidence of dementia in the HSV-infected subject and control groups, and the difference between the two groups were significant (log-rank test < 0.001, Fig. 1).

Table 2 shows the Cox regression analysis of the factors associated with the risk of developing dementia. The crude HR was 2.542 (2.331-2.771, $P < 0.001$, data not shown). After adjusting for age, sex, CCI scores, geographical area of residence, urbanization level of residence, and monthly income, the adjusted HR was 2.564 (95% CI 2.351-2.795, $P < 0.001$). Subjects with either non-genital or genital HSV infections were associated with an increased risk of overall dementia, in comparison to the non-HSV control group. HSV infections were associated with an increased risk in subjects with any type of dementia such as AD, VaD, or other dementia, when compared to the control group. The HSV-infected subjects were associated with overall increased risk in dementia even after we excluded individuals with a diagnosis of dementia within the first year and the first 5 years.

We have also analyzed the individual outcomes, as AD, VaD, and other dementia in Tables 3, 4, and 5, respectively. In general, the HSV subjects were associated with an increased risk in individual outcomes as AD, VaD, and other dementia. Furthermore, excluding those individuals with a diagnosis of dementia within the first year and the first 5 years, the HSV subjects were still associated with increased risk of individual types of dementia.

Supplementary Table 1 shows the sex, age, comorbidities, urbanization, area of residence, and the income of the HSV subjects with and without anti-herpetic medication treatment. Compared to the subjects without anti-herpetic medication treatment, the treated subjects tended to have a higher male to female ratio, CCI scores, residence in higher urbanization level, and living in northern Taiwan.

Subjects with HSV infections taking anti-herpetic medications ($N = 7215$) were compared to those patients not taking them ($N = 1147$). In the subgroup with anti-herpetic

Table 2 The risk of all dementias between HSV-infected cohort and comparison cohort

Model	All dementia cases		Dementia in the first year excluded		Dementia in the first 5 years excluded	
Characteristics	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
HSV infection (reference without)	2.564 (2.351-2.795)	< 0.001***	1.649 (1.443-1.869)	< 0.001***	1.646 (1.304-2.078)	< 0.001***
HSV-1 infection	2.588 (2.379-2.826)	<0.001***	1.679 (1.474-1.912)	< 0.001***	1.709 (1.354-5.159)	< 0.001***
HSV-2 infection	2.003 (1.832-2.197)	< 0.001***	0.751 (0.312-1.807)	0.522	0	0.890
Male (reference: female)	1.103 (1.023-1.189)	0.010*	1.083 (0.989-1.187)	0.086	1.066 (0.931-1.220)	0.356
≧ 65 years (reference: 50–64 years)	1.644 (1.45-1.859)	< 0.001***	1.789 (1.519-2.107)	< 0.001***	2.287 (1.708-3.062)	< 0.001***
Catastrophic illness card (reference: without)	1.193 (1.082-1.315)	< 0.001***	1.345 (1.193-1.516)	< 0.001***	1.324 (1.101-1.592)	0.003**
Insured premium (NT$) (reference < 18,000)						
18,000-34,999	0.443 (0.271-0.725)	0.001**	0.471 (0.273-0.814)	0.007**	0.802 (0.442-1.457)	0.470
≧ 35,000	0	0.829	0	0.862	0	0.911
Diabetes mellitus (DM) (reference: without)	0.923 (0.839-1.015)	0.098	0.950 (0.849-1.064)	0.378	0.961 (0.812-1.137)	0.642
Hypertension (reference: without)	0.864 (0.794-0.939)	0.001**	0.843 (0.763-0.931)	0.001**	0.828 (0.717-0.956)	0.010*
Hyperlipidemia (reference: without)	0.687 (0.524-0.900)	0.006**	0.728 (0.536-0.989)	0.043*	0.642 (0.405-1.017)	0.059
Coronary artery disease (CAD) (reference: without)	0.752 (0.665-0.852)	< 0.001***	0.709 (0.610-0.824)	< 0.001***	0.669 (0.534-0.837)	< 0.001***
Obesity (reference: without)	1.045 (0.147-7.425)	0.956	1.602 (0.225-11.394)	0.638	0	0.934
Cancer (reference: without)	0.380 (0.311-0.465)	< 0.001***	0.310 (0.238-0.403)	< 0.001***	0.392 (0.267-0.576)	< 0.001***
CCI_R	0.889 (0.870-0.908)	< 0.001***	0.981 (0.950-1.013)	0.248	0.948 (0.899-0.999)	0.046*
Urbanization level (reference: 4, the lowest)						
1 (The highest)	0.825 (0.742-0.917)	< 0.001***	0.818 (0.719-0.930)	0.002**	0.847 (0.700-1.025)	0.087
2	0.786 (0.713-0.866)	< 0.001***	0.790 (0.703-0.897)	< 0.001***	0.786 (0.661-0.936)	0.007**
3	0.855 (0.725-1.008)	0.062	0.846 (0.696-1.028)	0.092	0.901 (0.680-1.196)	0.472

HR = hazard ratio; CI = confidence intervals; Adjusted HR = adjusted for all variables in the table

Comparison between patients with or without HSV infections: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Table 3 The risk of Alzheimer dementia between HSV-infected cohort and comparison cohort

Model	All dementia cases		Dementia in the first year excluded		Dementia in the first 5 years excluded	
Characteristics	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
HSV infection (reference without)	2.739 (2.511-2.985)	< 0.001***	1.670 (1.009-2.233)	0.029*	1.648 (1.048-5.218)	0.044*
HSV-1 infection	2.799 (2.610–3.012)	< 0.001***	1.770 (1.053-2.323)	0.001**	1.709 (1.354-2.158)	< 0.001***
HSV-2 infection	0	0.961	0	0.980	0	0.890
Male (reference: female)	1.449 (0.730-2.879)	0.289	1.192 (0.759-1.870)	0.446	1.449 (0.730-2.879)	0.289
≧ 65 years (reference: 50–64 years)	2.158 (0.516-9.018)	0.292	1.431 (0.687-2.983)	0.338	2.158 (0.516-9.018)	0.292
Catastrophic illness card (reference: without)	0.783 (0.276-2.220)	0.645	1.068 (0.570-2.003)	0.837	0.783 (0.276-2.220)	0.645
Insured premium (NT$) (reference < 18,000)						
18,000-34,999	0	0.975	0	0.963	0	0.975
≧ 35,000	0	0.994	0	0.991	0	0.994
Diabetes mellitus (DM) (reference: without)	0.718 (0.316-1.633)	0.429	0.686 (0.376-1.250)	0.218	0.718 (0.316-1.633)	0.429
Hypertension (reference: without)	1.331 (0.678-2.612)	0.407	0.836 (0.512-1.364)	0.473	1.331 (0.678-2.612)	0.407
Hyperlipidemia (reference: without)	1.576 (0.362-6.856)	0.545	1.405 (0.432-4.574)	0.572	1.576 (0.362-6.856)	0.545
Coronary artery disease (CAD) (reference: without)	0.614 (0.211-1.784)	0.370	0.460 (0.197-1.073)	0.072	0.614 (0.211-1.784)	0.370
Obesity (reference: without)	0	0.996	0	0.994	0	0.996
Cancer (reference: without)	0.249 (0.032-1.915)	0.182	0.113 (0.019-0.667)	0.016*	0.249 (0.032-1.915)	0.182
CCI_R	1.079 (0.891-1.306)	0.437	1.025 (0.862-1.219)	0.777	1.079 (0.891-1.306)	0.437
Urbanization level (reference: 4, the lowest)						
1 (The highest)	1.522 (0.576-4.017)	0.397	0.820 (0.443-1.517)	0.527	1.552 (0.576-4.017)	0.397
2	0.988 (0.382-2.555)	0.980	0.786 (0.450-1.372)	0.397	0.988 (0.382-2.555)	0.980
3	0.902 (0.182-4.474)	0.899	0.431 (0.127-1.456)	0.175	0.902 (0.182-4.474)	0.899

AD = Alzheimer dementia; HR = hazard ratio; CI = confidence intervals; Adjusted HR: adjusted for all variables in the table

Comparison between patients with or without HSV infections: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Table 4 The risk of vascular dementia between HSV-infected cohort and comparison cohort

Model	All dementia cases		Dementia in the first year excluded		Dementia in the first 5 years excluded	
Characteristics	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
HSV infection (reference: without)	1.878 (1.344-2.624)	< 0.001***	1.694 (1.113-2.580)	0.014*	2.194 (1.163-4.137)	0.015*
HSV-1 infection	1.823 (1.293–2.571)	< 0.001***	1.624 (1.051-2.509)	0.029*	2.265 (1.201-4.272)	0.012*
HSV-2 infection	3.209 (1.022–10.080)	0.046*	3.574 (0.882-14.473)	0.074	0	0.996
Male (reference: female)	1.064 (0.822-1.378)	0.637	1.115 (0.830-1.498)	0.469	1.290 (0.845-1.970)	0.238
≧ 65 years (reference: 50-64 years)	3.527 (1.923–6.469)	< 0.001***	4.044 (1.897-8.621)	< 0.001***	3.977 (1.256-12.589)	0.019*
Catastrophic illness card (reference: without)	1.759 (1.290-2.398)	< 0.001***	1.773 (1.238-2.538)	0.002**	1.211 (0.675-2.172)	0.520
Insured premium (NT$) (reference < 18,000)						
18,000-34,999	0.635 (0.158-2.560)	0.523	0.762 (0.189-3.079)	0.703	1.383 (0.338-5.659)	0.652
≧ 35,000	0	0.957	0	0.962	0	0.973
Diabetes mellitus (DM) (reference: without)	1.153 (0.852-1.560)	0.356	1.134 (0.801-1.608)	0.478	0.941 (0.562-1.577)	0.819
Hypertension (reference: without)	1.174 (0.897-1.536)	0.242	1.054 (0.776-1.432)	0.737	0.844 (0.544-1.308)	0.448
Hyperlipidemia (reference: without)	1.465 (0.789-2.722)	0.226	1.854 (0.990–3.472)	0.054	1.640 (0.649-4.415)	0.292
Coronary artery disease (CAD) (reference: without)	0.558 (0.358-0.872)	0.010**	0.613 (0.377-0.996)	0.048*	0.646 (0.330-1.264)	0.202
Obesity (reference: without)	0	0.986	0	0.971	0	0.979
Cancer (reference: without)	0.034 (0.009-0.132)	< 0.001***	0.060 (0.015-0.234)	< 0.001***	0.115 (0.021-0.640)	0.014*
CCI_R	1.069 (0.966-1.184)	0.198	1.033 (0.915-1.165)	0.602	.1.008 (0.847-1.200)	0.928
Urbanization level (reference: 4, the lowest)						
1 (The highest)	1.195 (0.828-1.726)	0.341	1.089 (0.728-1.631)	0.678	0.849 (0.485-1.487)	0.567
2	0.945 (0.665-1.343)	0.751	0.799 (0.541-1.178)	0.257	0.648 (0.385-1.098)	0.107
3	0.606 (0.305-1.202)	0.152	0.559 (0.261-1.196)	0.134	0.727 (0.295-1.788)	0.487

VaD = Vascular dementia; HR = hazard ratio; CI = confidence intervals; Adjusted HR = adjusted for all variables in the table

Comparison between patients with or without HSV infections: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Table 5 The risk of other dementia between HSV-infected cohort and comparison cohort

Model	All dementia cases		Dementia in the first year excluded		Dementia in the first 5 years excluded	
Characteristics	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
HSV infection (reference: without)	1.974 (1.810-2.152)	< 0.001***	1.674 (1.458-1.922)	< 0.001***	1.607 (1.246-2.073)	< 0.001***
HSV-1 infection	2.760 (2.518-3.025)	< 0.001***	1.722 (1.499-1.978)	< 0.001***	1.670 (1.295-2.155)	< 0.001***
HSV-2 infection	1.808 (1.150-2.844)	0.010*	0.517 (0.166-1.605)	0.254	0	0.898
Male (reference: female)	1.109 (1.023-1.202)	0.012*	1.076 (0.975-1.187)	0.144	1.028 (0.899-1.190)	0.706
≧ 65 years (reference: 50-64 years)	1.556 (1.370-1.768)	< 0.001***	1.699 (1.430-2.018)	< 0.001***	2.172 (1.600–2.966)	< 0.001***
Catastrophic illness card (reference: without)	1.270 (1.143-1.410)	< 0.001***	1.311 (1.152-1.493)	< 0.001***	1.368 (1.122-1.667)	0.002**
Insured premium (NT$) (reference < 18,000)						
18,000-34,999	0.412 (0.239-0.711)	0.001**	0.463 (0.256-0.838)	0.011*	0.766 (0.396-1.482)	0.429
≧ 35,000	0	0.841	0	0.874	0	0.917
Diabetes mellitus (DM) (reference: without)	0.906 (0.818-1.004)	0.059	0.940 (0.832-1.063)	0.323	0.974 (0.811-1.170)	0.782
Hypertension (reference: without)	0.840 (0.768-0.919)	< 0.001***	0.820 (0.736-0.913)	< 0.001***	0.804 (0.687-0.940)	0.006**
Hyperlipidemia (reference: without)	0.601 (0.441-0.819)	0.001**	0.588 (0.408-0.848)	0.004**	0.514 (0.295-0.894)	0.019*
Coronary artery disease (CAD) (reference: without)	0.786 (0.690-0.896)	< 0.001***	0.739 (0.629-0.867)	< 0.001***	0.682 (0.353-0.870)	0.002**
Obesity (reference: without)	1.194 (0.180-8.484)	0.860	1.902 (0.267-13.524)	0.521	0	0.938
Cancer (reference: without)	0.441 (0.359-0.542	< 0.001***	0.359 (0.273-0.472)	< 0.001***	0.444 (0.297-0.668)	< 0.001***
CCI_R	0.960 (0.953-0.987)	0.004**	0.975 (0.942-1.010)	0.157	0.934 (0.882-0.990)	0.021*
Urbanization level (reference 4, the lowest)						
1 (The highest)	0.835 (0.745-0.935)	0.002**	0.790 (0.688-0.908)	0.001**	0.823 (0.668-1.012)	0.065
2	0.800 (0.721-0.888)	< 0.001***	0.789 (0.696-0.894)	< 0.001***	0.798 (0.661-0.963)	0.018*
3	0.909 (0.765-1.079)	0.275	0.905 (0.738-1.110)	0.340	0.943 (0.698-1.274)	0.702

HR = hazard ratio; CI = confidence intervals; Adjusted HR = adjusted for all variables in the table.

Comparison between patients with or without HSV infections: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Table 6 Percentage, duration, percentage of decrease of risk by days, and adjusted hazard ratio of anti-herpetic medications

Anti-herpetic medications				With *versus* without	
Type	*n* (%)	Duration (days)	*n* % decrease of risk/day	Adjusted HR (95% CI)	*P*
Over-all	7215	90.01 ± 121.78	1.009	0.092 (0.079-0.108)	< 0.001***
Acyclovir	1835 (25.43%)	91.32 ± 127.62	1.025	0.064 (0.028-0.083)	< 0.001***
1-29 days	1125 (15.59%)	26.54 ± 35.42	1.616	0.571 (0.254-0.895)	< 0.001***
≧ 30 days	710 (9.84%)	193.93 ± 273.71	0.500	0.031 (0.012-0.104)	0.007**
Famciclovir	1799 (24.94%)	86.25 ± 116.40	1.054	0.091 (0.075-0.100)	0.003**
1–29 days	997 (13.82%)	22.45 ± 32.45	1.804	0.595 (0.157-0.912)	0.014*
≧30 days	802 (11.12%)	165.56 ± 220.76	0.579	0.042 (0.022-0.089)	0.001**
Ganciclovir	698 (9.68%)	95.44 ± 129.08	0.810	0.227 (0.107-0.545)	0.015*
1–29 days	401 (5.56%)	27.72 ± 39.56	1.652	0.542 (0.264-0.988)	0.040*
≧ 30 days	297 (4.12%)	186.87 ± 249.95	0.506	0.055 (0.024-0.167)	0.007**
Valciclovir	842 (11.67%)	79.28 ± 118.53	1.068	0.153 (0.096-0.317)	0.001**
1-29 days	459 (6.36%)	20.79 ± 31.12	1.837	0.618 (0.154-0.997)	0.048*
≧ 30 days	383 (5.31%)	149.38 ± 223.29	0.603	0.099 (0.045-0.268)	< 0.001***
Valganciclovir	1977 (27.40%)	88.46 ± 120.74	1.034	0.085 (0.053-0.098)	< 0.001***
1-29 days	1013 (14.04%)	25.31 ± 36.78	1.671	0.577 (0.256-0.752)	< 0.001***
≧ 30 days	964 (13.36%)	154.82 ± 208.97	0.596	0.077 (0.032-0.091)	< 0.001***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

medications treatment, 419 (5.80%) developed dementia in the longitudinal follow-up within 10 years. In the subgroup without anti-herpetic medications treatment, 325 (28.33%) developed dementia in the same follow-up period. Anti-herpetic medications, either over-all (adjusted HR 0.092, 0.079-0.108, $P < 0.001$) or individual antivirals, were associated with decreased risk of developing dementia (Table 6). Table 6 also shows the percentages of these medications, the mean durations of medications, and the adjusted hazard ratios, percentage of the decrease of risk in each day of usage of antivirals, and the differences between the durations of antiviral treatment and the associations with the decrease of risk of dementia, by the over-all or individual anti-herpetic medications. Cumulative risk of dementia among patients with HSV infections aged 50 and over was stratified by anti-herpetic medication usage with log-rank test (log-rank test < 0.001, Fig. 2). Subjects with anti-herpetic treatment were associated with a decreased risk of overall dementia, AD, VaD, and other dementia. In addition, either genital or non-genital HSV infection in the subjects with anti-herpetic medications showed a decreased risk of dementia when compared to the group without anti-herpetic medications.

Discussion

In our study, HSV-infected subjects had an almost 3-fold increased risk of developing any type of dementia, including AD, VaD, or other dementia, in comparison to the control group. The Kaplan-Meier analysis revealed that HSV-infected patients had a significantly lower 10-year psychiatric disorders-free survival rate than the controls. In addition, it took 1 year to achieve a significantly adjusted HR, and therefore, 10 years appear to be a reasonable period to follow-up patients with HSV infections. Even though the individuals with a diagnosis of dementia within the first year and the first 5 years were excluded, the HSV-infected subjects were still associated with increased risk of individual types of dementia. Several previous local cohort studies revealed that seropositivity of HSV increased the risk of Alzheimer disease [26]. However, this is the first nationwide, matched cohort study for the association between both HSV types 1 or 2 infections and the risk of all types of dementia.

In this study, we defined at least three outpatient visits within the one-year study period for HSV infections according to these ICD-9-CM codes as the study cases. However, this probably means that only those with significant clinically visible symptoms of reactivations of HSV were selected. This is not a weakness of the method but probably a strength, which could in some way correspond to those of previous cohort studies indicating an increased risk with HSV IgM-antibodies as a measure of reactivated HSV infection, as previous researches have already pointed out [26, 27]. Furthermore, at least three crucial points validate the diagnostic specificity in this claims dataset based study: first, all clinicians used the ICD-9-CM codes in Taiwan; second, licensed medical records technicians verified the coding before claiming the reimbursements; and third, the National Health Insurance Administration authority verified the audit.

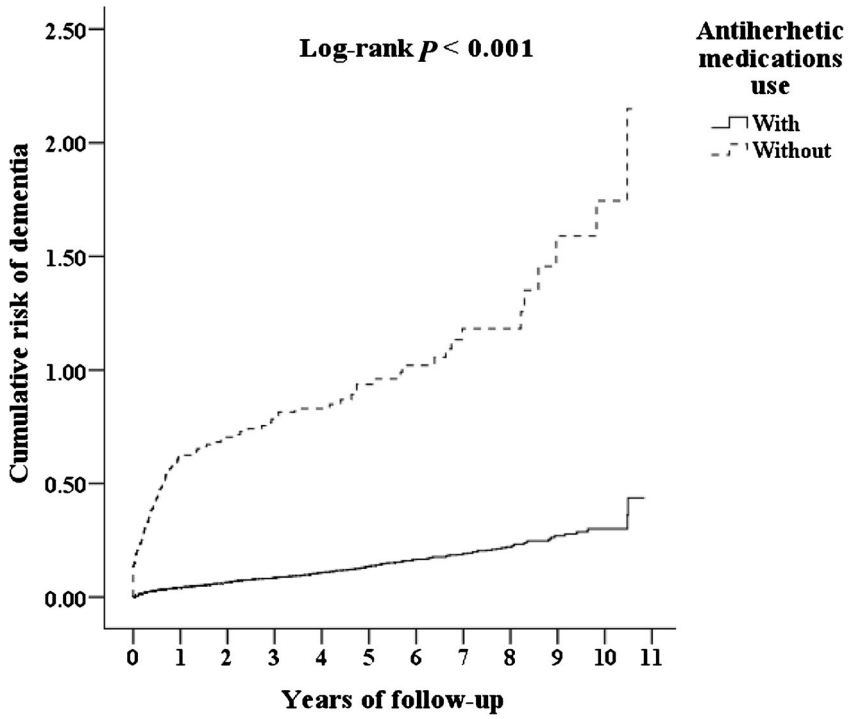

Fig. 2 Cumulative risk of dementia among HSV-infected patients aged 50 and over stratified by anti-herpetic medication use with log-rank test

The underlying mechanisms of the association between HSV infections and dementia remain unclear. Nonetheless, inflammatory changes in the brain have been reported in studies on the pathogenesis of dementia [28, 29], and previous researchers found that infectious diseases, such as hepatitis C viral infection, *Helicobacter pylori* infection, cytomegalovirus infections, chronic osteomyelitis, or even sepsis, were associated with an increased risk of dementia [30–34]. In 1982, Ball first suggested that HSV-1 might be involved in the pathogenesis of AD by finding that the brain regions damaged in HSV encephalitis, the limbic system, are the same as those affected the earliest in AD [35]. This is reinforced by the finding that receptors for HSV-1 are selectively expressed in the limbic system [36]. Several other studies have shown that HSV-1 and being a carrier of the apolipoprotein E allele 4 (ApoE e4) together confer risk for AD [9, 11, 27, 37–39]. Some studies have found that amyloid-β (Aβ) peptides have antiviral activity or protective effects against HSV infections in the brain by preventing the virus from fusing with the plasma membrane [40], and further suggested HSV infections as a possible risk factor for AD [41–43]. β-amyloid peptides have been found to have antimicrobial activity, including against HSV-1 [40, 44]. Previous studies have also shown that HSV-1 DNA is detected in AD plaques [45], HSV-1 infection-induced synaptic dysfunction via glycogen synthase kinase 3 (GSK-3) activation and intraneuronal amyloid-β protein accumulation [46], as well as the presence of intrathecal antibodies to HSV-1 [47]. Nevertheless, the potential pathogenetic link between HSV infections and the risk of other types of dementia, as shown in this study, remain unclear. Pro-inflammatory factors or oxidative stress might induce neuroinflammation and neurodegeneration and, thus, contribute to the pathogenesis of dementia [9, 48].

Previous studies have shown that the reactivation of HSV increases the risk for AD [26, 27]. In one study from Taiwan, the seroprevalence rate for HSV-1 infection reached 95.0% for those over 30 years of age, and for HSV-2, the rate was 31.2% for those over 60 years old [49]. Therefore, considering the high prevalence of latent HSV-1 in the population aged over 30, many of the "newly diagnosed" HSV-1 infections may represent reactivation of the virus, with positive immunoglobulin (IG) G and IgM, rather than a newly acquired primary HSV infection (IgG−, IgM+). One study also pointed out that cold sores, or herpes labialis, only occur in 20 to 40% of the population infected by HSV-1, and the other 60 to 80% of subjects might have been infected but not affected, that is, they were not symptomatic [50]. Furthermore, in our study, the adjusted HR was 2.564 for the risk of developing dementia in the HSV infection group, which is very close to the finding of the HR of 2.55 in the risk of developing AD in a previous study [27]. In our study, serology data was not available. Therefore, a future study using HSV serology is needed to confirm the association between re-activation of HSV and the risk of AD.

Moreover, we also found that anti-herpetic medications were associated with a lower risk of dementia in patients with HSV infections, and the adjusted HR was 0.092. This means that treatment with anti-herpetic medications could reduce

nearly 90.8% of the risk of developing dementia in patients with HSV infections. The HSV-infected subjects treated with anti-herpetic medications showed a decreased risk in all types of dementia such as AD, VaD, or other dementia, when compared to the group without anti-herpetic medications. In general, patients with shorter (< 30 days) or longer (≧ 30 days) durations of anti-herpetic medications were associated with a decreased risk of dementia, and the treatment duration of ≧ 30 days was associated with a lower risk of dementia than those of a duration of < 30 days. In the patients with ophthalmic or other specified complications, oral and intravenous anti-herpetic medications also showed the effects of reducing the risk of dementia in these patients.

The role of the anti-herpetic medication treatment for the prevention of AD have not been studied in the past, even though one author argued that antiviral agents in neurodegenerative disorders could be a new paradigm targeting AD [35]. Our study found that anti-herpetic medications could attenuate the risk of developing dementia (adjusted HR 0.092, 0.079-0.108, $P < 0.001$). One previous study demonstrated improvement in cognition of HSV-1 IgG seropositive schizophrenia patients with valacyclovir treatment for 18 weeks and compared it to a HSV-1 IgG seronegative control group in a clinical trial [51]. Our present study might be the first report on the role of anti-herpetic medication treatment in attenuating the risk of developing dementia for patients with HSV infections in a nationwide, population-based study. However, in the HSV-group, only 13.7% (1147 in 8362) did not receive anti-herpetic medications. This suggests that further study is needed to clarify whether anti-herpetic medication usage plays a role in reducing the risk of dementia for HSV-infected patients. Meanwhile, a clinical trial using valacyclovir for patients with early AD is ongoing in Sweden [52].

In addition, recent studies have reported trends in decreasing incidence of Alzheimer disease and other cognitive impairments since the late twentieth century, and researchers suggest that this results from increasing level of education and decreasing prevalence of cardiovascular comorbidities [53–57]. We also speculate that the introduction of anti-herpetic medications, for example, acyclovir [58], since the 1980s, could also contribute to this trend by decreasing the risk of dementia in HSV-infected patients.

In this study, we found that males are over-represented in the HSV-infected cohort (4724 males and 3638 females), a finding that is different from results seen in seroprevalence studies in Europe and North America, in which far more females than males are reported to have either HSV-1 or HSV-2 infections [59, 60]. However, a seroprevalence study of HSV-1 and HSV-2 in Taiwan found no significant association between sex and HSV-1 seropositivity, but females had higher rates of HSV-2 seropositivity, and overall age-weighted seropositive rate of HSV-1 and HSV-2 was 63.2% (95% CI, 60.6-65.7%), and 7.7% (95% CI, 6.2-9.5%), respectively [49]. We, therefore, speculate that the HSV-1 predominance in this study might result in the divergence of the sex ratio in this study in comparison to studies in Europe and North America. Furthermore, different study designs using claims dataset or seroprevalence data might also play an important role. However, the reasons for the difference among these studies remain unknown and need further investigation.

Limitations

There are several limitations to this study. First, patients with dementia could be identified using insurance claims data. However, data on the severity, stage, or impact on their caregivers were not available, and in such a study based on a claims dataset, we could only estimate treatment durations of each anti-herpetic medication by dividing the cumulative doses of individual medications by defined daily dose (DDD). The National Health Insurance Research Database (NHIRD) does not contain HSV serology data, either. Second, other residual confounding factors, such as education, genetics or dietary factors, are also not included in the NHIRD. Since there are no imaging findings or other laboratory data included in the NHIRD, we could only rely on the professional diagnosis of dementia by board-certified psychiatrists or neurologists as aforementioned. Furthermore, several community studies have revealed that Alzheimer dementia is the most common cause of dementia (40-60% in all dementias), followed by vascular dementia (20-30% in all dementias), and mixed or other dementias (7-15%) in Taiwan [1, 61, 62], whereas most of the dementias in our study were other types. One possible hypothesis is that some of the other dementias might actually be AD cases. Another possibility is that clinicians might put these types of dementia with a progressive course and no evidence of previous cerebrovascular events into this category instead of AD. In addition, the NHIRD does not have data on APOE-e4 genotype, which is not only a risk for AD in Taiwan and other countries [63–65], but also increases the frequency of symptomatic oral herpetic lesions [38] without viral shedding [38, 66]. Further studies are, therefore, warranted to determine the APOE genotypes in HSV-infected patients and controls.

Conclusions

Patients with HSV infections may have a 2.56-fold increased risk of developing dementia. The usage of anti-herpetic medications in the treatment of HSV infections was associated with a decreased risk of dementia. These findings might well be a signal to the clinicians caring for patients with HSV infections. Further research is necessary to explore the underlying mechanism(s) of this association.

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Compliance with Ethical Standards

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

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