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Herpes zoster associated with stroke incidence in people living with human immunodeficiency virus: a nested case–control study

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Abstract

Background The incidence of stroke is increasing among younger people with human immunodeficiency virus (HIV). The burden of stroke has shifted toward the young people living with HIV, particularly in low- and middle-income countries. People infected with herpes zoster (HZ) were more likely to suffer stroke than the general population. However, the association of HZ infection with the incidence of stroke among patients with HIV remains unclear.

Methods A nested case–control study was conducted with patients with HIV registered in the Taiwan National Health Insurance Research Database in 2000–2017. A total of 509 stroke cases were 1:10 matched to 5090 non-stroke controls on age, sex, and date of first stroke diagnosis. Logistic regression models were used to estimate the odds ratio and 95% confidence intervals (CI) of stroke incidence.

Results The odds ratio of stroke was significantly higher in the HIV-infected population with HZ (adjusted odds ratio [AOR]: 1.85, 95% CI: 1.42–2.41). A significantly increased AOR of stroke was associated with hypertension (AOR: 3.53, 95% CI: 2.86–4.34), heart disease (AOR: 2.32, 95% CI: 1.54–3.48), chronic kidney disease (AOR: 1.82, 95% CI: 1.16–2.85), hepatitis C virus infection (AOR: 1.49, 95% CI: 1.22–1.83), hyperlipidemia (OR: 1.41, 95% CI: 1.12–1.78), and treatment with protease inhibitors (AOR: 1.33, 95% CI: 1.05–1.69).

Conclusions Our findings suggest that HZ concurrent with HIV may increase the risk of stroke. The incidence rates of stroke were independent of common risk factors, suggesting strategies for early prevention of HZ infection among people living with HIV.

Keywords Nested case–control study, Stroke, Incidence, HIV, Herpes zoster, Taiwan National Health Insurance Research Database

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Introduction

Stroke is the second most common cause of death resulting in a significant health burden worldwide [1]. In 2019, global stroke incidence increased by 70%, its mortality by 43%, and disability-adjusted life-years (DALYs) due to stroke by 32% [2]. An increasing number of individuals are experiencing hemorrhagic stroke with an 80% mortality rate at a younger age in low- and middle-income countries [3, 4].

Given the increased global access to antiretroviral therapy (ART), neurological conditions are becoming more frequent in the aging population with longstanding human immunodeficiency virus (HIV) infection, including cerebrovascular disease (CVD) and peripheral neuropathy [5]. Patients who suffer HIV-induced stroke tend to be younger and more immunocompromised than the general population [6, 7]. People living with HIV (PLWH) in Europe and America have a greater risk of stroke than the general population [8–12]. Chronic inflammation and immune activation, typically observed in elderly people and termed "inflammaging," can occur in HIV-infected patients who experience a unique type of premature aging, which significantly affects their quality of life [13, 14].

HIV-associated vasculopathy encompasses several pathologic phenotypes of stroke found in PLWH [15–17]. This may be due to chronic systemic inflammation, which occurs despite virological suppression and due to long-term ART toxicity, lifestyle factors, or a combination thereof [18, 19]. Two systematic reviews and meta-analyses reported an increased risk of ischemic stroke post-herpes zoster (HZ) infection in younger individuals and those not prescribed antivirals [20, 21]. Male sex, hypertension, metabolic factors, older age, alcohol/drug abuse, HIV RNA, high viral load, and CD4 count < 200 cells/μL have more strongly predicted ischemic stroke [9, 10, 22, 23]. Conversely, HZ infection, male sex, cardiovascular history, hypertension, smoking, injecting drug users (IDU), hepatitis C, and estimated glomerular filtration (eGFR) rate < 60 mL/min/m^3 and CD4 count < 200 cells/μL have strongly predicted hemorrhagic stroke [8, 22, 24, 25]. A pilot study in Uganda reported that an HIV-infected population with varicella zoster virus antibodies had a three-fold higher risk of stroke [26].

Herpes zoster (shingles) is caused by the reactivation of the varicella-zoster virus (VZV), which typically remains latent after primary infection with varicella (chickenpox) during childhood. Chickenpox is characterized by vesicular lesions on an erythematous base in different stages of development; lesions are most concentrated on the face and trunk [27]. The presenting clinical manifestations of herpes zoster are usually rash and acute neuritis. HZ (shingles) is caused by the first VZV, which remains latent in the sensory ganglia following varicella infection [28]. HZ is largely considered to be a once-in-a-lifetime experience, up to 20 percent of people will develop shingles during their lifetime. HZ recurrence is thought to be limited to immunocompromised individuals and is an HIV-associated opportunistic infection. Herpes zoster (HZ) infection is a risk factor for stroke. People with HZ infection were found to be more likely to suffer stroke than the general population with the incidence rate ratios (IRRs) for all patients and patients aged 18 to 49 years were 1.40 and 8.12, respectively [29]. An analysis of records from the Taiwan National Health Research Institute revealed a 30% increase in the risk of stroke among the general population within 1 year of having an HZ infection [24]. Furthermore, the relationship between the HZ infection and the risk of stroke among people with HIV infection remains unclear.

This study aimed to estimate the odds ratio of stroke in association with HZ among PLWH. In the present study, we used the linked data obtained from the Taiwan National Health Insurance database to conduct a population-based, nested case–control study. The primary objective was to investigate the potential association between HZ infection and an elevated risk of stroke incidence. Additionally, we sought to contrast the occurrence of stroke events in HIV-infected patients both with and without a history of HZ infection.

Methods

Data source

Patient data were retrieved from medical claims of Taiwan's National Health Insurance (NHI) program. The NHI released de-identified secondary data to the public for research purposes. Access to the NHI medical claims was approved by the Review Committee of Health and Welfare Data Science Center, Ministry of Health and Welfare. Our study was approved by the Research Ethics Committee of Tainan Municipal An-Nan Hospital-China Medical University (approval number TMANH109-REC024). The NHI medical claims cover claims data of > 99% of Taiwan residents [30]. Emergency, outpatient, and inpatient medical claims of all diagnosed HIV-infected persons from 2000 to 2018 were retrieved from the NHI medical claims. Data linkages among various medical claim datasets were allowed using de-identified personal identification numbers.

Nested case–control design and participants

The case–control study was nested within 35,168 patients with HIV who had ≥ 1 admission or ≥ 2 ambulatory care visits for primary HIV diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]) code: 042–044.9, V08; (International

Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]) code: B20-B24, Z21, Z22.6) within a 365-day period in 2002–2016. The following HIV patients were excluded: Patients with HIV aged < 18 years old or unknown sex ($n = 699$). In measuring the 2-year period of case management follow-up, patients diagnosed with HIV in 2000 and 2001 were excluded ($n = 2{,}769$). A final total of 31,707 patients with HIV was included in the study population.

Selection of cases and controls

We estimated the incidence of stroke in HIV-infected patients who had their first emergency visit or hospitalization for stroke events in the period from the date of the initial diagnosis (i.e., index date) to the end of the follow-up period, date of death, or December 31, 2017. By modifying the coding algorithm proposed by Hsieh et al., [31] the incidence of major stroke events is defined as the first occurrence of strokes in this study, including ischemic stroke (ICD-9-CM: 433.xx, 434.xx, and ICD-10-CM: I63), hemorrhagic stroke (ICD-9-CM: 430, 431, and ICD-10-CM: I60, I61) and transient ischemic attack (TIA) (ICD-9-CM: 435.xx, and ICD-10-CM: I60-64, G45) in emergency or inpatient medical records from the first clinical visit for HIV to the end of the observation period [32, 33]. A total of 509 patients aged ≥ 18 years and with an incident stroke were identified. In our study, the diagnosis of HIV followed by the occurrence of stroke indeed constitutes a rare event. We have opted for a larger matching ratio of 1:10. This choice aligns with our goal of enhancing comparability and minimizing potential biases between the two groups. For patients with stroke, ten controls were randomly selected using propensity score matching to identify the stroke ($n = 590$) and non-stroke ($n = 5{,}090$) groups by matching stroke cases on sex, age (± 5 years), and month of stroke diagnosis. After propensity score matching, including the month of diagnosis, age (± 5 years) at diagnosis, and sex, were comparable between the stroke and non-stroke groups.

The date of the first-ever stroke diagnosis in 2002–2017 was considered as the index date for each patient with stroke and his/her matched controls. Therefore, an individual who was selected as a control could later become a stroke case. In all, 5,090 matched control subjects were selected.

The HZ group included all patients who had ≥ 1 admission or ≥ 2 ambulatory care visits before the first stroke event after HZ diagnosis (ICD-9-CM: 053.0–053.11, 053.19–053.9, and ICD-10-CM: B02.xx) events were identified based on the medical claims of inpatient or outpatient department. These patients were required to have at least two outpatients (within 7 days apart) or inpatient visits for HZ after the initial HIV diagnosis. The incidence of HZ was defined as 1 month after an HIV diagnosis because most of the people living with HIV infection had a concurrent HZ infection at the time of diagnosis. Based on the incidence of HZ within the 1-year period between the enrollment and index dates, we further categorized the study subjects into four groups, namely, stroke patients with and without HZ and controls with and without HZ. A flow chart of the patient enrollment process is illustrated in Fig. 1.

Confounders

Demographic and risk factors were also retrieved from the claims data, including age at the date of the first HIV and stroke diagnoses, geographic area, and monthly income after the HIV diagnosis. Patients' demographic characteristics, including age, sex, income, and residential area, were retrieved from beneficiary records. The urbanization level for each 316 city/township in Taiwan was determined using Liu et al.'s method which classified all cities and townships in Taiwan into different urbanization levels based on various indicators [34]. The median family annual income of each city/township was used to indicate the neighborhood socioeconomic of status for each study patient. Monthly income-based insurance premium was categorized into three levels with cut-off points of < 20,000 New Taiwan dollars (NTD) (< 660.50 USD), 20,000–40,000 NTD (660.50–1321.00 USD), and > 40,001 NTD (> 1321.04 USD) (1 USD = 30.28 NTD, Exchange Rate for Individual Income Tax Return from Year 2015 to Year 2022).

Various comorbidities were considered as risk factors for stroke: hypertension, diabetes mellitus, hyperlipidemia, CVD, coronary artery disease, myocardial infarction, heart failure, atrial fibrillation, chronic kidney disease, hepatitis B virus (HBV), and hepatitis C virus (HCV) (Supplemental Table 1). Each comorbidity was identified following the relevant ICD-9-CM or ICD-10-CM codes presented in three outpatient claims within 1 year before the index date.

Since 2015, the World Health Organization has recommended that PLWH undergo ART, irrespective of CD4 count or clinical stage. The ART regimen groups were classified into three groups: non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), and protease inhibitors (PIs). To mitigate potential confounding effects, we diligently excluded patients concurrently receiving both NNRTIs and PIs regimens during the drug selection process. These groups were based on stable users (defined as continuous use for up to ≥ 6 months) after the ART initiation. Patients who received ART more than 6 months before the index date of stroke occurrence were defined as ART users. Baseline antiviral medications for HZ

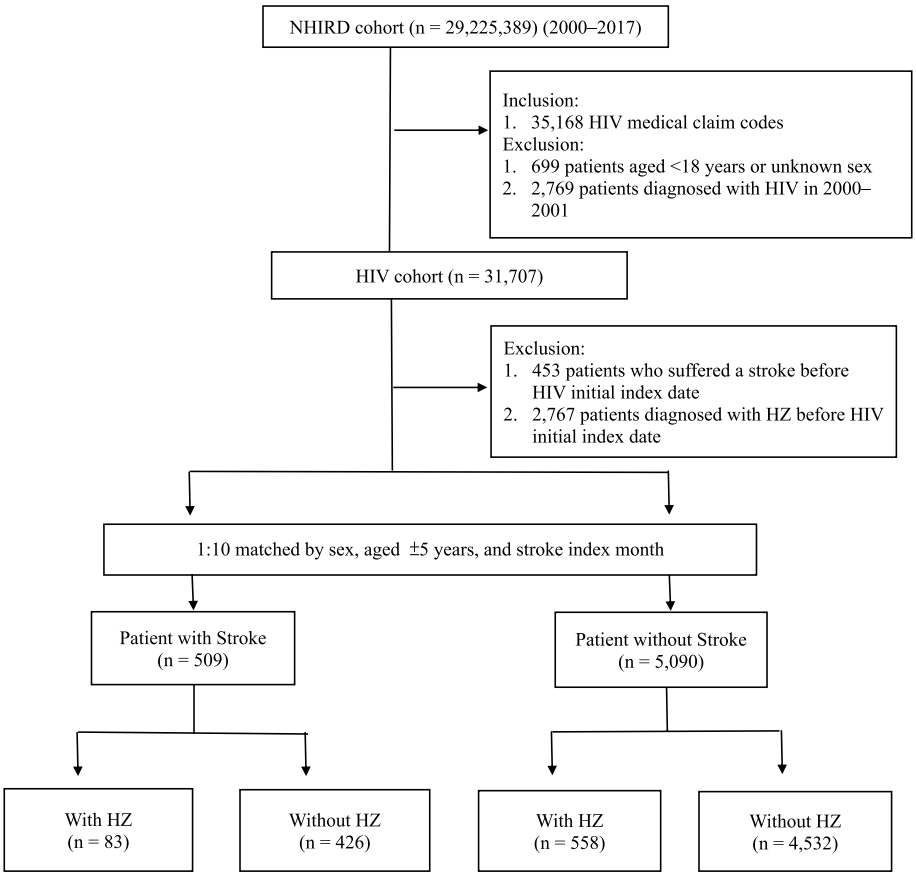

Fig. 1 Flow chart of patient selection for the case and control groups

were recorded as acyclovir, valacyclovir, and famciclovir administered for 7–10 days. We retrieved information on all acyclovir (ATC code: J05AB01), valacyclovir (ATC code: J05AB11), and famciclovir (ATC code: J05AB09) prescriptions.

Statistical analysis

First, the difference between the characteristics of the stroke and control groups was assessed using the chi-squared test. To examine the correlation between the risk of stroke in people living with HZ, the crude odds ratios (ORs), covariate-adjusted odds ratios (AORs), and 95% confidence intervals (CIs) were calculated from conditional logistic regression analysis. The regression model was created to investigate whether exposure to HZ may pose a duration effect on the risk of stroke incidence. The ORs and AORs were also used to estimate the relative stroke risk at various time points after determining the duration of HIV infection and concurrent HIV and HZ infection. The potential confounders adjusted for in the multivariate regression model included all variables listed in Table 1. All statistical analyses were performed using the SAS version 9.4 software (SAS Institute, Cary, NC, USA). A p-value of < 0.05 was considered statistically significant.

Results

From January 1, 2000, to December 31, 2017, a total of 509 cases diagnosed with HIV infection who had strokes were investigated, whereas 5,090 controls with HIV who had not suffered from a stroke at the index date were considered as controls, showing that study patients with stroke tended to be young, living in urban areas, and earning lesser wages. The mean ages were similar for the patients and controls at 46.14 years and 45.73 years, respectively. Male patients accounted for 90.96% and 91.77% of patients and controls, respectively. The area of residence and monthly income varied significantly among people with HIV infection who suffered from stroke ($p < 0.0001$). Approximately 43.81% of PLWH who suffered a stroke had received ART, with PIs (22.79%) as the primary medications. The age, sex, insurance premium, and income level are comparable in patients and controls in this study. However, compared with controls, patients were more likely to have a history of comorbidities, including alcohol-related illness, hypertension,

Table 1 Characteristics of patients and controls

Variable	Cases (stroke) (*n* = 509) n (%)	Controls (non-stroke) (*n* = 5,090) n (%)	*p*-value
Age (years)			0.98
18–34	80 (15.72)	805 (15.81)	
35–44	159 (31.24)	1591 (31.26)	
45–54	160 (31.43)	1644 (32.30)	
55–64	84 (16.50)	787 (15.46)	
≥ 65	26 (5.11)	263 (5.17)	
Mean (SD)	46.14 (11.17)	45.73 (11.11)	
Sex			0.53
Female	46 (9.04)	419 (8.23)	
Male	463 (90.96)	4671 (91.77)	
Geographic area			**< 0.001**
North	236 (46.37)	2773 (54.48)	
Central	112 (22.00)	985 (19.35)	
South	158 (31.04)	1248 (24.52)	
East	3 (0.59)	84 (1.65)	
Monthly income, USD			**< 0.001**
< 660.50	333 (65.42)	2368 (46.52)	
660.50–1321.00	148 (29.08)	1840 (36.15)	
> 1321.04	28 (5.50)	882 ((17.33)	
Comorbidity			
Hypertension	273 (53.63)	1338 (26.29)	**< 0.001**
HCV	230 (45.19)	1597 (31.38)	**< 0.001**
Hyperlipidemia	152 (29.86)	1191 (23.40)	**0.001**
HBV	100 (19.65)	897 (17.62)	0.26
Heart disease	41 (8.06)	122 (2.40)	**< 0.001**
Diabetes mellitus	40 (7.86)	292 (5.74)	0.053
Chronic kidney disease	33 (6.48)	133 (2.61)	**< 0.001**
Coronary artery disease	15 (2.95)	94 (1.85)	0.087
Alcohol-related illness	15 (2.95)	78 (1.53)	0.017
PAOD	5 (0.98)	14 (0.28)	**0.009**
AMI	0 (0)	16 (0.31)	-
ART regimen			
PIs	116 (22.79)	889 (17.47)	**0.003**
NRTIs	88 (17.29)	878 (17.25)	0.98
NNRTIs	17 (3.73)	123 (2.42)	0.20

SD Standard deviation, *USD* United States Dollars, *HCV* Hepatitis C virus, *HBV* Hepatitis B virus, *PAOD* Peripheral arterial occlusive disease, *AMI* Acute myocardial infarction, *ART* Antiretroviral therapy, *PIs* Protease inhibitors, *NRTIs* Nucleoside reverse transcriptase inhibitors, *NNRTIs* Non-nucleoside reverse transcriptase inhibitors

hyperlipidemia, peripheral arterial occlusive disease, heart disease, chronic kidney disease, and HCV (Table 1).

Table 2 shows the crude ORs, AORs, and 95% CIs for the risk of stroke in PLWH in Taiwan. After controlling the potential confounders including sex, age, geographic area, monthly income, and comorbidity, results of multivariate logistic regression analysis were compared to that of controls, and the people with HIV infection with HZ (AOR: 1.85, 95% CI: 1.42–2.41), hypertension (AOR: 3.53, 95% CI: 2.86–4.34), heart disease (AOR: 2.32, 95% CI: 1.54–3.48), chronic kidney disease (AOR: 1.82, 95% CI: 1.16–2.85), hyperlipidemia (AOR: 1.41, 95% CI: 1.12–1.78), HCV (AOR: 1.49, 95% CI: 1.22–1.83) and taking PIs (AOR: 1.33, 95% CI: 1.05–1.69) have a significantly higher risk of stroke.

Table 3 shows the crude ORs and AORs for stroke risk based on the duration of concurrent HIV and HZ infection. After controlling the potential confounders,

Table 2 Odds ratios of the risk of stroke in PLWH in Taiwan

Variables	Controls (non-stroke) (*n* = 5,090)	Cases (stroke) (*n* = 509)	Crude OR (95% CI)	*p*-value	Adjusted OR[a] (95% CI)	*p*-value
HZ						
No	4,532 (89.04%)	426 (83.69%)	Reference		Reference	
Yes	558 (10.96%)	83 (16.31%)	1.58 (1.23–2.03)	**< 0.001**	1.85 (1.41–2.41)	**< 0.001**
Sex						
Female	419 (8.23%)	46 (9.04%)	Reference		Reference	
Male	4,671 (91.77%)	463 (90.96%)	0.90 (0.66–1.24)	0.53	0.91 (0.65–1.27)	0.59
Age						
18–34	805 (15.82%)	80 (15.72%)	Reference		Reference	
35–44	1,591 (31.26%)	159 (31.24%)	1.01 (0.76–1.33)	0.96	0.76 (0.56–1.02)	**0.003**
45–54	1,644 (32.29%)	160 (31.43%)	0.98 (0.74–1.30)	0.72	0.54 (0.39–0.73)	0.45
55–64	787 (15.46%)	84 (16.50%)	1.07 (0.78–1.48)	0.56	0.44 (0.30–0.63)	**0.02**
≥ 65	263 (5.17%)	26 (5.11%)	0.99 (0.63–1.58)	0.93	0.35 (0.21–0.58)	**0.007**
Geographic area						
North	2,773 (54.48%)	236 (46.37%)	Reference		Reference	
Central	985 (19.35%)	112 (22.00%)	1.34 (1.05–1.69)	**0.04**	0.92 (0.81–1.33)	0.24
South	1,248 (24.52%)	158 (31.04%)	1.49 (1.20–1.84)	**0.007**	1.24 (0.99–1.55)	**0.02**
East	84 (1.65%)	3 (0.59%)	0.46 (0.13–1.34)	0.06	0.38 (0.12–1.30)	0.1
Monthly income, USD						
< 660.50	2,368 (46.52%)	333 (65.42%)	Reference		Reference	
660.50–1321.00	1,840 (36.15%)	148 (29.08%)	0.57 (0.47–0.70)	0.16	0.56 (0.45–0.70)	0.3
> 1321.04	882 (17.33%)	28 (5.50%)	0.23 (0.15–0.33)	**< 0.001**	0.24 (0.16–0.36)	**< 0.001**
Comorbidity						
Alcohol-related illness						
No	5,012 (98.47%)	494 (97.05%)	Reference		Reference	
Yes	78 (1.53%)	15 (2.95%)	1.95 (1.11–3.42)	**0.02**	1.30 (0.72–2.36)	0.39
Hypertension						
No	3,752 (73.71%)	236 (46.37%)	Reference		Reference	
Yes	1,338 (26.29%)	273 (53.63%)	3.24 (2.70–3.90)	**< 0.001**	3.53 (2.86–4.34)	**< 0.001**
Diabetes mellitus						
No	4,798 (94.26%)	469 (92.14%)	Reference		Reference	
Yes	292 (5.74%)	40 (7.86%)	1.40 (0.99–1.98)	**0.05**	0.72 (0.49–1.08)	0.11
Hyperlipidemia						
No	3,899 (76.60%)	357 (70.14%)	Reference		Reference	
Yes	1,191 (23.40%)	152 (29.86%)	1.39 (1.14–1.70)	**0.001**	1.41 (1.12–1.78)	**0.003**
PAOD						
No	5,076 (99.72%)	504 (99.02%)	Reference		Reference	
Yes	14 (0.28%)	5 (0.98%)	3.60 (1.29–10.04)	**0.01**	2.61 (0.83–8.17)	0.1
Coronary artery disease						
No	4,996 (98.15%)	494 (97.05%)	Reference		Reference	
Yes	94 (1.85%)	15 (2.95%)	1.61 (0.93–2.80)	0.09	1.12 (0.60–2.09)	0.72
Heart disease						
No	5,626 (97.60%)	468 (91.94%)	Reference		Reference	
Yes	122 (2.40%)	41 (8.06%)	3.57 (2.47–5.15)	**< 0.001**	2.32 (1.54–3.48)	**< 0.001**
Chronic kidney disease						
No	4,957 (97.39%)	476 (93.52%)	Reference		Reference	
Yes	133 (2.61%)	33 (6.48%)	2.58 (1.75–3.83)	**< 0.001**	1.82 (1.16–2.85)	**0.01**
HBV						
No	4,193 (82.38%)	409 (80.35%)	Reference		Reference	
Yes	897 (17.62%)	100 (19.65%)	1.14 (0.91–1.44)	0.26	1.06 (0.83–1.36)	0.63

Table 2 (continued)

Variables	Controls (non-stroke) (*n* = 5,090)	Cases (stroke) (*n* = 509)	Crude OR (95% CI)	*p*-value	Adjusted OR[a] (95% CI)	*p*-value
HCV						
No	3,493 (68.62%)	279 (54.81%)	Reference		Reference	
Yes	1,597 (31.38%)	230 (45.19%)	1.80 (1.50–2.17)	**< 0.001**	1.49 (1.22–1.83)	**< 0.001**
ART regimen						
Only NRTIs						
No	4,212 (82.75%)	421 (82.71%)	Reference		Reference	
Yes	878 (17.25%)	88 (17.29%)	1.00 (0.79–1.28)	0.98	0.99 (0.74–1.31)	0.93
Only NNRTIs						
No	4,967 (97.97%)	492 (96.66%)	Reference		Reference	
Yes	123 (2.03%)	17 (3.34%)	1.40 (0.83–2.34)	0.2	1.25 (0.68–2.29)	0.47
Only PIs						
No	4,181 (82.14%)	393 (77.21%)	Reference		Reference	
Yes	889 (17.86%)	116 (22.79)	1.40 (1.12–1.74)	**0.003**	1.33 (1.05–1.69)	**0.02**

PLWH People living with HIV, *OR* Odds ratio, *HZ* Herpes zoster, *USD* United States Dollars, *PAOD* Peripheral arterial occlusive disease, *AMI* Acute myocardial infarction, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *ART* Antiretroviral therapy, *NRTIs* Nucleoside reverse transcriptase inhibitors, *NNRTIs* Non-nucleoside reverse transcriptase inhibitors, *PIs* Protease inhibitors

[a] Odds ratios were calculated from the logistic regression model adjusted for age, sex, geographic area, monthly income, comorbidity, and ART regimen

Table 3 Odds ratios for stroke risk of the duration of concurrent HIV and HZ infection

Duration of concurrent HZ infection	Non-stroke cases	Stroke cases	OR (95% CI)	*p*-value	Adjusted OR[a] (95% CI)	*p*-value
≤ 3 months	110	15	1.00 (Reference)		1.00 (Reference)	
> 3 and ≤ 6 months	88	9	1.08 (0.54,2.15)	0.58	1.45 (0.71,2.97)	0.97
> 6 months	360	59	1.73 (1.29,2.31)	**0.02**	2.04 (1.49,2.78)	**0.03**

HZ Herpes zoster, *OR* Odds ratio, *CI* Confidence interval

[a] Odds ratios were calculated from the logistic regression model adjusted for age, sex, area of residence, monthly income, comorbidity, and highly active antiretroviral therapy regimen (NNRTIs, NRTIs, PIs)

the duration of concurrent HIV and HZ infection at > 3 and ≤ 6 months (AOR: 1.45, 95% CI: 0.71, 2.97), and > 6 months (AOR: 2.04, 95% CI: 1.49, 2.78) showed a higher risk of stroke.

Discussion

This is the first population-based study reporting an elevated 1.85-fold risk of stroke in patients with HZ among PLWH. Our study finding is consistent with two cohort studies in America that reported that the stroke incidence was 2.26–5.27 per 1,000 person-years among people living with HIV [9, 35].

Our finding showed that male sex and not receiving ART were the major risk factors for HZ among HIV-infected patients. The majority of stroke occurrence in people living with HIV and HZ patients were men, which differ from the observation made in other studies [5, 9, 36], indicating that stroke among people with HIV infection occurred mostly in women. The majority of people with HIV were men due to the demographics of the HIV-infected population in Taiwan. However, the adjusted hazard ratio of stroke among male and female patients during the 1-year follow-up period was 1.30–1.32 times higher ($p < 0.05$) than that of patients with HZ [24]. In addition, Gutierrez et al. demonstrated that a CD4 count < 200, longer duration of HIV infection, and prior history of stroke were all associated with large-artery atherosclerosis, whereas small-vessel disease was associated with CD4 count > 200, no history of prior cardiac disease, and male sex [37]. Future research is needed to elucidate the pathophysiology of HIV, HZ, and stroke risk and investigate sex differences in stroke risk.

The main age group of people with HIV infection suffering from stroke were in the 35–44 and 45–54 age groups. The results of multivariate logistic regression analysis revealed that people with HIV infection aged 35–44, 55–64, and more than 65 years have a significantly lower

risk of stroke, which were inconsistent with those of other studies reporting that a higher incidence of stroke occurs among younger people with HIV infection [9, 16, 36]. Most HZ-associated vasculopathy develop within 6 weeks after HZ events [36]. In the general population, younger people (0–49 years) had a higher risk of developing stroke or TIA within 1 year after HZ diagnosis [38]. Neurological conditions, including stroke, are occurring at a younger age in people with chronic HIV infection, a phenomenon referred to as accelerated aging. This may due to chronic inflammation, which occurs despite virological suppression and due to long-term ART toxicity, lifestyle risk factors, or a combination of the above [5, 19].

Our study has shown a significantly increased risk of stroke following an HIV infection, particularly due to comorbidities such as hypertension, hyperlipidemia, heart disease, chronic kidney disease, HCV, and treatment with PIs. Moreover, the risk of stroke is higher among people with HIV infection with hypertension, a finding consistent with the results of other studies [23, 34, 36, 39]. People with HIV infection have a significantly higher risk of stroke due to comorbidities, such as heart disease and chronic kidney disease, which is consistent with that of the general population. Among the people with HIV infection who underwent ART, particular treatment with PIs, low-density cholesterol, smoking, and high-density cholesterol are associated with heart diseases [23, 36].

Our study indicated that the overall risk of stroke was significantly increased with > 6 months of concurrent HIV and HZ infection. HZ-associated vasculopathy is also defined as follows: (1) induced production of prothrombotic autoimmune antibodies, (2) autoimmune phenomena caused by circulating immune complexes, and (3) disrupted internal elastic lamina, intimal hyperplasia, and decreased smooth muscle cells in the tunica media layer [40, 41]. HIV-associated vasculopathy or histologic evidence of extensive atherosclerosis was observed in relatively younger patients who started ART in the 6 months prior to their stroke event [42]. The rates of stroke were significantly increased within 1 week to 3 months after HZ diagnosis. However, the risk was reduced gradually and resolved after over 1 year [43–45]. Nevertheless, the underlying mechanism of the risk of stroke in concurrent HZ and HIV remains unclear. This should be evaluated in future clinical studies.

This key strength of this study is advantageous because it is a nested case–control study, a research design combining the advantages of case–control and cohort studies. It retains the advantages of the case–control study that saves manpower, material resources, and time, and has the advantage of a cohort study to determine the relationship between exposure and causality. In addition, both the patient and control groups are retracted from the same generational group of patients with HIV, which reduces the sample selection bias. During the process, matched methods are used to randomly select the control group, which improves the statistical efficiency. Few studies have focused on the HZ-induced risk of stroke among people with HIV infection in the ART era.

This study has limitations. First, the secondary health insurance database was analyzed. The potential of missing coding or coding errors may result in misclassifications. Nevertheless, such issues would result in a biased association toward the null effect, thereby underestimating the predictive power of our study. Second, the test data such as viral load and CD4 index and the lack of characterization of stroke pathology were not collected. Therefore, the patient's immune status, ART compliance with medication, correlation with stroke, and excluding the subset of stroke cases cannot be assessed. Prospective studies can be conducted to assess the relationship between the side effects of using ART and stroke in the future. Furthermore, HIV infection and HZ infection can both induce stroke. We cannot exclude the possibility that there may be a common risk factor for the occurrence of HZ and stroke in the PLWH population. Intermediary analysis can be used to explore the relationship between two diseases and stroke.

Conclusions

In conclusion, this is the first study in Asia to analyze the risk of stroke in people with HIV infection with HZ from 2000 to 2017. A 1.85-fold increased risk of stroke was observed in patients with HZ among the people with HIV infection. A significantly elevated risk of stroke was found in PLWH with hypertension, heart disease, chronic kidney disease, hyperlipidemia, HCV, and treatment with PIs. Further studies are needed to clarify the relationships between HIV, HZ, and stroke. Clinicians and people with HIV infection should be aware of the risk factors of stroke among PLWH. The results of this study can be used as a basis by which health policymakers can determine appropriate stroke prevention programs for people living with HIV and HZ, as well as to help them formulate and implement regulations related to controlling for risk factors of stroke and stroke prevention among people living with HIV and HZ.

Supplementary Information

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Additional file 1: Supplementary Table 1. Operation definitions for study outcomes. **Supplementary Figure 1.** Overview of the participant selection process.

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Authors' contributions
HCK, CYL, HTO and NYK initially conceived of the study, with HCK, CYL, HTO and NYK contributing to the study design. HCK, HTY, YLW, CYL and NYK supported acquiring and interpreting the data, while HCK and HTY were involved in the analysis. The manuscript was prepared by HCK and NYK, and all authors contributed to revision of the manuscript and approved the final version.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Declarations

Ethics approval and consent to participate
The Institutional Review Board (IRB) of Tainan Municipal An-Nan Hospital China Medical University (TMANH) approved this study (TMANH109-REC024), and was conducted in accordance with the principles of the Declaration of Helsinki. The study utilized data from the National Health Insurance (NHI) Research Database in Taiwan, which is maintained by the National Health Research Institutes (NHRI). The use of this database was approved by the NHRI and the Bureau of National Health Insurance. Since the datafile contained only de-identified secondary data, the institutional review board of TMANH waived the requirement for informed consent. All methods in this study were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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