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Hepatitis C virus infection as a risk factor for Parkinson disease

A nationwide cohort study

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ABSTRACT

Objective: To determine whether hepatitis C virus (HCV) infection is a risk factor for developing Parkinson disease (PD).

Methods: This nationwide population-based cohort study was based on data obtained from a dataset of the Taiwan National Health Insurance Research Database for the period 2000 to 2010. A total of 49,967 patients with viral hepatitis were included for analysis. Furthermore, 199,868 people without viral hepatitis were included for comparisons. Patients with viral hepatitis were further grouped into 3 cohorts: hepatitis B virus (HBV) infection, HCV infection, and HBV-HCV coinfection. In each cohort, we calculated the incidence of developing PD. A Cox proportional hazards model was applied to estimate the risk of developing PD in terms of hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: The crude HRs for developing PD was 0.66 (95% CI = 0.55–0.80) for HBV infection, 2.50 (95% CI = 2.07–3.02) for HCV infection, and 1.28 (95% CI = 0.88–1.85) for HBV-HCV coinfection. The association between HCV and PD remained statistically significant after adjustments for age, sex, and comorbidities (adjusted HR = 1.29, 95% CI = 1.06–1.56).

Conclusions: We conducted a large nationwide population-based study and found that patients with HCV exhibit a significantly increased risk of developing PD. ***Neurology*® 2016;86:1–7**

GLOSSARY

BBB = blood–brain barrier; **CI** = confidence interval; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; **LHID** = Longitudinal Health Insurance Database; **NHI** = National Health Insurance; **NHIP** = National Health Insurance Program; **NHIRD** = National Health Insurance Research Database; **PD** = Parkinson disease; **PS** = propensity score.

Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by the early prominent death of dopaminergic neurons in the substantia nigra pars compacta,[1] leading to movement disorders characterized by bradykinesia, muscular rigidity, rest tremor, postural imbalance, and gait impairment.[2] PD is considered the most common neurodegenerative disorder after Alzheimer disease, and its incidence rate ranges from 10 to 18 per 100,000 person-years.[3]

Emerging evidence shows that the hepatitis C virus (HCV) is neurotropic and can replicate in the CNS.[4–6] Chronic HCV infection is often associated with cognitive dysfunction, fatigue, and depression.[4] Parkinsonism is rarely a described feature in patients with HCV. However, a recent study has discovered that HCV can induce dopaminergic neuron death, suggesting a possible association between HCV infection and PD.[7]

In the current nationwide cohort study, we determined whether HCV infection is a risk factor for developing PD. We selected 249,835 people from the Taiwan National Health Insurance (NHI) database to investigate the association between hepatitis infection and PD.

Supplemental data at Neurology.org

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METHODS **Data source.** The National Health Insurance Program (NHIP) is a mandatory single-payer program established by the Taiwan Bureau of National Health Insurance. The NHIP covers more than 99% of the residents of Taiwan. The National Health Insurance Research Database (NHIRD) comprises claims data of patients enrolled in the NHIP. The Longitudinal Health Insurance Database (LHID), which is one of the NHIRD datasets, comprises data for 1 million insurants randomly selected from the original 1996–2000 NHI registry. The LHID contains all medical records for each insurant from 1996 to 2011. The identities of the insurants in the LHID are recoded before their release to researchers. In this LHID, disease identification was based on the *ICD-9-CM*.

Standard protocol approvals, registrations, and patient consents. Because of the Personal Information Protection Act, this study was approved to fulfill the condition for exemption by the institutional review board of China Medical University (CMUH104-REC2-115). The institutional review board also specifically waived the consent requirement.

Patients. Patients newly diagnosed with hepatitis B virus (HBV) (*ICD-9-CM* 070.20, 070.22, 070.30, 070.32, and V02.61) and HCV (*ICD-9-CM* 070.41, 070.44, 070.51, 070.54, and V02.62) infection from 2000 to 2010 were included (n = 52,771). The date of viral hepatitis infection was defined as the index date. Patients who were (1) aged younger than 20 years (n = 2,182) or (2) had PD or parkinsonism history (*ICD-9-CM* 322.XX, n = 622) recorded before the index date were excluded. The patients were grouped into 3 cohorts according to the virus type: HBV infection, HCV infection, and HBV-HCV coinfection. Four controls frequency matched as case cohorts (n = 199,868) were selected from people without viral hepatitis or those who satisfied the exclusion criteria. The frequency matched criteria included age stratum (such as 20–24, 25–29 years and so on), sex, and index year.

Endpoint and comorbidity. All patients were followed from the index date until the date of PD (*ICD-9-CM* 332.0X) development. Those without PD development were followed until the date of withdrawal from the NHIP or until the end of 2011. We also assessed comorbidities (*ICD-9-CM*), including hyperlipidemia (272.XX), hypertension (401.XX–405.XX), ischemic heart disease (410.XX–414.XX), epilepsy (345.XX), diabetes (250.XX), cirrhosis (571.2X), stroke (430.XX–438.XX), and head injury (850.XX–854.XX, 959.01). All comorbidities were defined before the index date.

Sensitivity test. Propensity score (PS)-matched analysis was used for the sensitivity test. PS for each study participant was counted by logistic regression with the following variables: age, sex, index year, and comorbidities containing hypertension, hyperlipidemia, ischemic heart disease, epilepsy, diabetes, cirrhosis, stroke, and head injury. According to the nearest-neighbor PS, 2 patients with HBV and 2 controls for each patient with HCV were selected in PS1 and PS2 studies, respectively.

Statistical analysis. The distributions of age (20–34, 35–49, 50–64, and ≥65 years), sex, and comorbidity between each of the 3 viral hepatitis cohorts and control cohort were compared using the χ^2 test. The incidence of PD (per 10,000 person-years) was calculated in each cohort. We estimated the risk of developing PD and associated risk factors by using Cox proportional hazard regression. Hazard ratios (HRs) were also adjusted using a multivariate model. Furthermore, in each cohort, we assessed the risks of developing PD stratified by age, sex, and comorbidity status, as well as the association between PD and the risk factors. A Kaplan-Meier analysis was conducted to plot the disease-free probability, and a log-rank test was applied to test the difference between each cohort. For PS-matched cohorts, matched Cox proportional hazard regression was used to estimate the risk of developing PD. We executed all data analyses by using the SAS version 9.3 statistical software package (SAS Institute Inc., Cary, NC). The level of significance was set to $p < 0.05$ for a 2-tailed test.

RESULTS Table 1 shows the demographic data and comorbidities for the patients with viral hepatitis and controls. Among 49,967 patients with viral hepatitis, 35,619 (71.3%) had HBV infection, 10,286 (20.6%) had HCV infection, and 4,062 (8.1%) had both HBV and HCV infections. The mean age of the hepatitis cohort and controls was 46.4 (±15.3 years) and 46.2 (±15.6 years), respectively. Approximately 43.5% of the patients were women, which was not different among the various hepatitis groups and controls. Compared with the controls, a higher percentage of patients with hepatitis exhibited comorbidities, namely, hyperlipidemia (19.3% vs 14.4%, $p < 0.0001$), hypertension (25.6% vs 21.4%, $p < 0.0001$), ischemic heart disease (12.5% vs 9.73%, $p < 0.0001$), epilepsy (0.75% vs 0.62%, $p = 0.002$), diabetes (8.64% vs 7.93%, $p < 0.0001$), liver cirrhosis (6.8% vs 0.77%, $p < 0.0001$), and head injury (10.1% vs 8.37%, $p < 0.0001$).

During the 12-year follow-up, the difference in the overall incidence for developing PD between the patients with hepatitis and controls was not significant (91.16 vs 85.55 per 10,000 person-years), with the crude HR being 1.06 (95% confidence interval [CI] = 0.93–1.22). Among those with hepatitis infection, the HR for having PD was 0.66 (95% CI = 0.55–0.80) for HBV, 2.50 (95% CI = 2.07–3.02) for HCV, and 1.28 (95% CI = 0.88–1.85) for HBV-HCV coinfection, respectively (table 2). After adjustments for age, sex, hyperlipidemia, hypertension, ischemic heart disease, epilepsy, diabetes, cirrhosis, stroke, and head injury, the association between HCV and PD remained statistically significant (adjusted HR = 1.29, 95% CI = 1.06–1.56). Figure e-1 on the *Neurology*® Web site at Neurology.org shows the proportion of PD-free patients in the 3 hepatitis cohorts.

Table 3 shows the incidence of PD in the various hepatitis cohorts stratified by age, sex, or comorbidity. A positive association between HCV and PD was maintained in patients aged younger than 65 years, males, or with a combination of any of the comorbidities (hyperlipidemia, hypertension, ischemic heart disease, epilepsy, diabetes, liver cirrhosis, stroke, or head injury).

Overall, in either the hepatitis cohorts or controls, age served as a universal risk factor for having PD (table 4). In the controls, most of the comorbidities

Table 1 Distribution of age, sex, and comorbidity between hepatitis infection and comparison cohort

	Hepatitis infection					
	Total (n = 49,967)	HBV (n = 35,619)	HCV (n = 10,286)	Both (n = 4,062)	Comparison (n = 199,868)	*p* Value[a]
Age, y						0.99
20–34	13,206 (26.4)	11,335 (31.8)	1,182 (11.5)	689 (17.0)	52,824 (26.4)	
35–49	17,338 (34.7)	13,539 (38.0)	2,518 (24.5)	1,281 (31.5)	69,352 (34.7)	
50–64	12,562 (25.1)	7,743 (21.7)	3,503 (34.1)	1,316 (32.4)	50,248 (25.1)	
65+	6,861 (13.7)	3,002 (8.43)	3,083 (30.0)	776 (19.1)	27,444 (13.7)	
Mean (SD)	46.4 (15.3)	43.3 (14.1)	55.4 (15.4)	50.7 (14.9)	46.2 (15.6)	
Sex						0.99
Women	21,729 (43.5)	14,800 (41.6)	5,122 (49.8)	1,807 (44.5)	86,916 (43.5)	
Men	28,238 (56.5)	20,819 (58.5)	5,164 (50.2)	2,255 (55.5)	112,952 (56.5)	
Comorbidity						
Hyperlipidemia	9,631 (19.3)	6,142 (17.2)	2,558 (24.9)	931 (22.9)	28,863 (14.4)	<0.0001
Hypertension	12,771 (25.6)	6,997 (19.6)	4,394 (42.7)	1,380 (34.0)	42,799 (21.4)	<0.0001
Ischemic heart disease	6,227 (12.5)	3,226 (9.06)	2,314 (22.5)	687 (16.9)	19,446 (9.73)	<0.0001
Epilepsy	373 (0.75)	222 (0.62)	118 (1.15)	33 (0.81)	1,248 (0.62)	0.002
Diabetes	5,709 (11.4)	3,077 (8.64)	2,022 (19.7)	610 (15.0)	15,841 (7.93)	<0.0001
Cirrhosis	3,396 (6.80)	1,745 (4.90)	1,203 (11.7)	448 (11.0)	1,539 (0.77)	<0.0001
Stroke	1,189 (2.38)	531 (1.49)	526 (5.11)	132 (3.25)	4,472 (2.24)	0.06
Head injury	5,061 (10.1)	3,163 (8.88)	1,413 (13.7)	485 (11.9)	16,722 (8.37)	<0.0001

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus.
Data represent n (%) unless otherwise indicated. χ^2 test.
[a] Total hepatitis infection vs comparison.

were associated with an increased risk of having PD; however, in those with HCV infection, only ischemic heart disease (HR = 1.65, 95% CI = 1.11–2.45) and head injury (HR = 2.03, 95% CI = 1.32–3.13) remained statistically significant.

For the sensitivity analysis, we selected 19,908 (6,636 HCV and 13,272 HBV patients) and 30,828 (10,286 HCV and 20,572 controls) participants in PS1 and PS2 studies (table e-1). There were similar results for the distribution of age, sex, and all comorbidities in PS1 and PS2 studies (standardized mean difference <0.1). Table 5 shows the incidence and HR for PD in PS1 and PS2 studies. In the PS1 study, patients with HCV infection had a higher PD incidence than patients with HBV without statistical significance (64.06 vs 55.56 per 10,000 person-years, HR = 1.31, 95% CI = 0.74–2.32). In the PS2 study, patients with HCV infection had a significantly higher incidence (213.84 vs 192.13 per 10,000 person-years) and risk (HR = 1.36, 95% CI = 1.04–1.77) than controls.

DISCUSSION HCV is a small, enveloped RNA virus belonging to the family *Flaviviridae* and genus *Hepacivirus*. Exposure to the virus in most cases leads to chronic infection, causing a progressive liver disease including hepatic fibrosis, cirrhosis, and hepatocellular carcinoma.[8] The seroprevalence of HCV has a significant geographical variation, ranging from 0.5% to 24.3% because of different contributions of risk factors in different study regions.[9] In developed countries, the HCV is transmitted largely by injection from illicit drug use.[10] In Taiwan, the prevalence of anti-HCV seropositivity is approximately 5%, and a history of blood transfusion is the most important risk factor for the HCV infection.[11]

Although HCV mainly targets hepatocytes, its involvement in extrahepatic tissue has been frequently reported.[12,13] The neurotropic characteristic of HCV is still controversial. Fletcher et al.[14] recently indicated that essential HCV receptors including CD81, claudin-1, occluding, LDLR, and scavenger receptor-B1 were expressed on the brain microvascular endothelial cells, a major component of the blood–brain barrier (BBB). This result suggested that HCV infection might compromise the BBB integrity, implying the entry of CNS. This result was also supported by the detection of negative-strand HCV RNA sequence in 6 postmortem brain tissue samples obtained from patients with HCV infection.[5] These findings confirm the extrahepatic target for HCV

Table 2 Incidence and HR for Parkinson disease and associated risk factors

				HR (95% CI)	
	Event no.	Person-years	Rate	Crude	Adjusted
Hepatitis infection					
None	1,060	1,234,235	85.88	1.00	1.00
All	270	296,198	91.16	1.06 (0.93-1.22)	1.12 (0.98-1.29)
HBV	121	213,762	56.60	0.66 (0.55-0.80)[a]	1.03 (0.85-1.25)
HCV	120	56,117	213.84	2.50 (2.07-3.02)[a]	1.29 (1.06-1.56)[b]
Both	29	26,318	110.19	1.28 (0.88-1.85)	0.97 (0.67-1.40)
Age, y					
20-49	80	992,212	8.06	1.00	1.00
50-64	366	363,680	100.64	12.7 (9.98-16.2)[a]	9.64 (7.52-12.3)[a]
65+	884	174,540	506.47	65.2 (51.8-81.9)[a]	38.4 (30.0-49.1)[a]
Sex					
Women	635	669,833	94.80	1.17 (1.05-1.31)[c]	1.08 (0.97-1.20)
Men	695	860,600	80.76	1.00	1.00
Comorbidity					
Hyperlipidemia					
No	850	1,316,338	64.57	1.00	1.00
Yes	180	214,095	224.20	3.51 (3.14-3.93)[a]	1.18 (1.05-1.33)[c]
Hypertension					
No	436	1,225,081	35.59	1.00	1.00
Yes	894	305,351	292.78	8.35 (7.44-9.36)[a]	157 (1.37-1.80)[a]
Ischemic heart disease					
No	821	1,390,394	59.05	1.00	1.00
Yes	509	140,039	363.47	6.22 (5.57-6.95)[a]	1.22 (1.08-1.38)[c]
Epilepsy					
No	1,313	1,521,870	86.28	1.00	1.00
Yes	17	8,563	198.53	2.32 (1.44-3.75)[a]	1.32 (0.81-2.14)
Diabetes					
No	1,009	1,417,668	71.17	1.00	1.00
Yes	321	112,765	284.66	4.05 (3.57-4.60)[a]	1.21 (1.06-1.38)[c]
Cirrhosis					
No	1,281	1,508,928	84.89	1.00	1.00
Yes	49	21,505	227.86	2.72 (2.05-3.62)[a]	1.23 (0.91-1.65)
Stroke					
No	1,198	1,505,486	79.58	1.00	1.00
Yes	132	24,947	529.12	6.81 (5.69-8.16)[a]	1.36 (1.13-1.64)[c]
Head injury					
No	1,181	1,419,693	83.19	1.00	1.00
Yes	149	110,739	134.55	1.64 (1.39-1.95)[a]	1.25 (1.05-1.48)[b]

Abbreviations: CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio.
Rate, per 10,000 person-years.
[a] $p < 0.001$.
[b] $p < 0.05$.
[c] $p < 0.01$.

Table 3 Incidence and HR for Parkinson disease stratified by age, sex, and comorbidity

	Comparison		Hepatitis infection									
			Total (n = 49,967)			HBV (n = 35,619)			HCV (n = 10,286)			Both (n = 4,062)		
	Event no.	Rate	Event no.	Rate	HR (95% CI)	Event no.	Rate	HR (95% CI)	Event no.	Rate	HR (95% CI)	Event no.	Rate	HR (95% CI)
Age, y														
<65	341	31.28	105	39.53	1.06 (0.85–1.32)	58	28.91	0.90 (0.68–1.19)	37	86.38	1.61 (1.13–2.28)[b]	10	45.03	0.92 (0.49–1.73)
65+	719	499.34	165	540.11	1.03 (0.86–1.22)	63	478.88	0.93 (0.71–1.20)	83	624.92	1.17 (0.93–1.48)	19	462.04	0.87 (0.55–1.38)
Sex														
Women	510	94.69	125	95.24	1.05 (0.86–1.28)	48	53.21	0.91 (0.67–1.22)	61	211.90	1.21 (0.92–1.59)	16	130.62	1.02 (0.62–1.69)
Men	550	79.06	145	87.91	1.19 (0.99–1.44)	73	59.09	1.13 (0.88–1.45)	59	215.88	1.38 (1.05–1.82)[a]	13	92.40	0.90 (0.52–1.59)
Comorbidity														
None	212	25.33	27	15.83	0.93 (0.62–1.39)	17	12.43	0.98 (0.59–1.61)	6	27.48	0.72 (0.32–1.63)	4	33.54	1.18 (0.44–3.16)
With any one	848	213.51	243	193.40	1.14 (0.99–1.32)	104	135.12	1.02 (0.83–1.25)	114	332.55	1.36 (1.12–1.66)[b]	25	173.71	0.92 (0.62–1.36)

Abbreviations: CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio.
[a] $p < 0.05$.
[b] $p < 0.01$.

infection, and HCV may directly induce neuropathology in vivo.

A possible association between HCV and parkinsonism was discovered. A previous study revealed that dopaminergic neurotransmission is altered in patients with HCV infection.[15] HCV was also reported to induce dopaminergic neuronal toxicity in the midbrain cell culture in rats.[7] From the epidemiology perspective, a recent study on a community-based cohort in Taiwan concluded that patients with anti-HCV(+) exhibited a significantly increased risk of developing PD.[7] Similarly, in the current study, which was conducted using larger samples in a nationwide population-based cohort, we observed that HCV infection was significantly associated with PD and that this infection could be one of its risk factors. This association was not observed in HBV infection or HBV-HCV coinfection. However, there were too few cases of HBV-HCV coinfection with PD development to attach the statistical difference.

The risk of developing PD is obviously multifactorial. Similar to several neurodegenerative disorders, age is a clear risk factor for developing PD and they were reported to exhibit an adequately established causal relationship.[16] In our study, we confirmed that age was a consistent risk factor for developing PD. Sex is another well-established risk factor, with studies reporting that men tend to have a higher incidence of PD than women do[17,18]; however, we did not observe this trend in our current study. Environmental exposures such as pesticide and previous head injury have also been considered as a possible risk factor for PD.[1,16]

A study proposed that a potential "second hit" might lead to the development of viral parkinsonism,[19] suggesting that environmental exposures or other risk factors also have a role in this condition. In our study, the most significant association between HCV and PD was observed in patients who were younger (aged younger than 65 years), male, or exhibited a combination of any of the comorbidities. The male sex or the comorbidities may serve as a second hit in our patient group, but the significant association between HCV and PD in the young age group indicates the possibility of HCV as a potential individual risk factor in patients aged younger than 65 years. Some of the risk factors for HCV infection, such as illicit drug use and associated behaviors, may be confounding factors in this age group. In Taiwan, the use of IV drugs is not one of its risk factors based on previous epidemiologic study, and history of blood transfusion is the most important risk factor for the HCV infection.

In addition to Lewy bodies, neuroinflammation is a characteristic feature of PD pathology.[16,20] Both microglia and astrocyte activation may result in

Table 4 Risk factors for Parkinson disease in patients with different hepatitis infections

Risk factor	None	HBV	HCV	Both
Age	1.10 (1.10–1.11)[a]	1.09 (1.07–1.11)[a]	1.08 (1.06–1.10)[a]	1.12 (1.08–1.16)[a]
Sex (women vs men)	1.06 (0.94–1.19)	1.25 (0.87–1.81)	1.17 (0.81–1.67)	0.85 (0.40–1.78)
Hyperlipidemia	1.25 (1.09–1.44)[b]	1.24 (0.84–1.82)	0.79 (0.52–1.19)	0.60 (0.25–1.47)
Hypertension	1.53 (1.31–1.78)[a]	2.34 (1.48–3.71)[a]	1.49 (0.94–2.37)	0.79 (0.34–1.85)
Ischemic heart disease	1.19 (1.03–1.36)[c]	0.89 (0.58–1.35)	1.65 (1.11–2.45)[c]	2.96 (1.31–6.72)[b]
Epilepsy	1.20 (0.68–2.13)	0.87 (0.12–6.39)	1.90 (0.59–6.07)	6.34 (0.70–57.2)
Diabetes	1.23 (1.06–1.44)[b]	1.03 (0.66–1.62)	1.13 (0.75–1.71)	1.32 (0.56–3.14)
Cirrhosis	1.67 (1.10–2.55)[c]	0.98 (0.49–1.94)	1.10 (0.65–1.87)	0.44 (0.10–1.86)
Stroke	1.37 (1.11–1.68)[b]	1.79 (0.93–3.42)	1.24 (0.69–2.21)	0.42 (0.05–3.66)
Head injury	1.13 (0.92–1.39)	1.01 (0.54–1.89)	2.03 (1.32–3.13)[b]	2.03 (0.75–5.52)

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus.
[a] $p < 0.001$.
[b] $p < 0.01$.
[c] $p < 0.05$.

reactive gliosis within areas of neurodegeneration in PD.[21] The release of numerous inflammatory mediators is known to disrupt BBB patency and allow entry of immune cells of the adaptive immune system into the CNS.[22,23] The role of peripheral immune cell influx has not been completely explored. Several studies implicated that effector T cells cause microglial activation and are neurotoxic.[24–26] In contrast, regulatory components of adaptive immunity affect neural repair and protection.[27,28]

Factors that trigger neuroinflammation in PD are debatable. Although a few studies have suggested that viral infection could elicit an inflammatory response in PD, a specific virus has not yet been formally identified.[29] The findings of the current study suggested that HCV is a possible candidate. An earlier imaging study that involved using magnetic resonance spectroscopy to investigate the cerebral effect of HCV showed that chronic HCV infection was associated with elevated choline/creatinine ratios, a biomarker indicating inflammatory and infective conditions, in the basal ganglia and white matter.[6] Additional clinical studies are required to confirm the association between HCV infection, neuroinflammation, and PD.

This study had limitations. First, we used *ICD-9-CM* codes, instead of clinical assessment, laboratory data, or neuroimaging study, for identifying PD and viral hepatitis profiles. This may lead to less accurate results, but all insurance claims in NHIRD were scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria. Second, the LHID does not contain information regarding the duration of viral hepatitis and some of the risk factors for HCV infection (blood transfusion, illicit drug use, tattooing, etc.). These factors for HCV infection might have confounding effects on PD development, but could not be controlled for analysis in the current study. In addition, evidence derived from a retrospective cohort study is typically lower in statistical quality because of numerous sources of inherent bias such as medical surveillance bias and misclassification bias.

In the current study, we found a significantly increased risk of developing PD in patients with HCV infection using a large nationwide population-based cohort. Additional clinical studies investigating the link between HCV infection and PD are warranted.

Table 5 Incidence and HR for Parkinson disease in hepatitis C infection compared to comparison cohort after PS matching

	PS1		PS2	
	HCV	HBV	HCV	Comparison
Event no.	25	44	120	233
Person-years	79,187	39,028	56,117	121,271
Rate	55.56	64.06	213.84	192.13
HR (95% CI)	1.31 (0.74–2.32)	1.00 (ref.)	1.36 (1.04–1.77)[a]	1.00 (ref.)

Abbreviations: CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio; PS = propensity score; ref. = reference.
Rate, per 10,000 person-years.
[a] $p < 0.05$.

AUTHOR CONTRIBUTIONS

Conception and design: Hsin-Hsi Tsai, Ruoh-Fang Yen, and Chia-Hung Kao. Administrative support: Chia-Hung Kao. Collection and assembly of data: Hsin-Hsi Tsai, Horng-Huei Liou, Chih-Hsin Muo, Cha-Ze Lee, Ruoh-Fang Yen, and Chia-Hung Kao. Data analysis and interpretation: Hsin-Hsi Tsai, Horng-Huei Liou, Chih-Hsin Muo, Cha-Ze Lee, Ruoh-Fang Yen, and Chia-Hung Kao. Manuscript writing: Hsin-Hsi Tsai, Horng-Huei Liou, Chih-Hsin Muo, Cha-Ze Lee, Ruoh-Fang Yen, and Chia-Hung Kao. Final approval of manuscript: Hsin-Hsi Tsai,

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DISCLOSURE

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