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Association between viral hepatitis infection and Parkinson's disease: A population-based prospective study

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Abstract

The association between hepatitis virus infection and Parkinson's disease remains controversial. To determine whether hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are associated with an increased risk of Parkinson's disease in Korean aged ≥40 years, we completed a population-based prospective study including patients without infections and those with HBV, HCV and HBV/HCV infections from 2005 to 2015. We used the International Classification of Diseases 10th Revision to identify Parkinson's disease (G20) and chronic hepatitis C virus (B18.2) and chronic hepatitis B virus infections (B18.0 or B18.1). To identify Parkinson's disease risk, competing risk analysis adjusted for age, sex, comorbidities and death was performed. Overall, 1 010 317 patients (358 052, noninfection; 488 990, hepatitis B; 144 459 hepatitis C; and 18 680 hepatitis B/C) were included. The incidence density of Parkinson's disease per 10 000 person-years was highest in the hepatitis C group (8.0), followed by the hepatitis B/C (6.8) and hepatitis B (5.0) groups. Hypertension, ischaemic heart disease, epilepsy, stroke and depressive disorder increased the hazard of Parkinson's disease in all groups. The adjusted hazard ratios were 1.25 (95% confidence interval: 1.17-1.35), 1.39 (95% confidence interval: 1.27-1.52) and 1.46 (95% confidence interval: 1.14-1.85) in the HBV, HCV, and HBV/HCV groups, respectively. Our findings suggest that adult patient of 40 years and older with HBV and HCV infections should be monitored for signs of Parkinson's disease so that early intervention and accurate treatment can be provided for minimizing the development and consequences of Parkinson's disease.

KEYWORDS

competing risk, Parkinson's disease, prospective studies, Viral hepatitis B, Viral hepatitis C

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; NHI, National Health Insurance; NHIS, National Health Insurance Service; NSC, National Sample Cohort; OR, odds ratio; PD, Parkinson's disease; TLR, toll-like receptor.

Hwa Young Choi and Ha Thi Mai contributed equally to the paper.

1 | INTRODUCTION

Parkinson's disease (PD) is the most common movement disorder and the second most common degenerative disease of the central nervous system, diagnosed in more than 10 million people worldwide.[1,2] The risk factors for PD are multifactorial that include genetic and environmental factors, such as advanced age, male sex or toxins.[2] In men, the risk of PD was found to be 1.5 times higher than that in women.[3] Interestingly, the number of men and women developing PD increases proportionally with age, suggesting that PD aetiology changes with age.[4]

Currently, some studies on the associations among hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection and PD have shown HCV infection to be consistently associated with an increased risk of PD. At least 1 year post-HCV infection, the rate ratio for PD was 1.43 in England, the odds ratio (OR) for PD was 1.39 in Taiwan, and the hazard ratio (HR) of PD was 1.29 in Taiwan.[5-7] However, the association between HBV infection and PD remains controversial. A recent study by Pakpoor et al[5] illustrated that HBV infection caused a 1.82-fold increase in PD risk compared to that in a reference cohort, whereas the association between HBV infection and PD was not found to be statistically significant in other studies.[6,8]

In 2015, of the 257 million people with chronic HBV infection and 71 million people with chronic HCV infection worldwide, 887 000 and 399 000 people died (mostly from complications including cirrhosis and hepatocellular carcinoma), respectively.[8] The increase in the ageing population in South Korea suggests a high risk of PD in the future as advancing age is one of the most important risk factors of PD. In 2016, the percentage of seniors aged ≥65 years in South Korea reached 13% (approximately 7 million) of the whole population and is predicted to increase to >40.1% in 2060 (Statistics Korea). According to our survey of the literature, no population-based prospective study has been conducted to demonstrate the relationships among HBV, HCV and PD; therefore, we believe that the current study might be the first population-based study of its kind.

We hypothesized that HBV and HCV infections are associated with an increased risk of PD. This study was designed to test this hypothesis by addressing two specific aims: (a) to determine the incidence of PD among participants with HBV or HCV infections; (b) to determine the associations of HBV and HCV infections with PD. Pursuing these aims will help in better understanding of the epidemiology of PD among the Korean population as well as in evaluating the effects of HBV and HCV infections on the development of PD.

2 | METHODS

2.1 | Data source

We used health insurance claims data provided by the Korea National Health Insurance Service (NHIS). The data included details of medical treatment (diagnosis, length of stay, treatment costs, services received, drug code, days prescribed and daily dosage) prescriptions and socio-economic (income-based insurance contributions, demographic variables and date of death characteristics) of inpatient and outpatient who joined the National Health Insurance (NHI) system.[9] In Korea, NHI is mandatory; it covered approximately 98% of the Korean population in 2015.[10] We used both the NHI data for all Korean populations to collect information about patients with viral hepatitis, and data from the NHIS-National Sample Cohort (NSC) to select participants without viral hepatitis. The NHIS-NSC cohort database contains data of 1 020 340 individuals (a 2.2% sample) stratified by sex, age, and income level and selected by random sampling from the 2002 target population of 4 6605 433 individuals. The selected individuals were followed for 11 years until 2013.[11] Based on the current National Health Insurance Act, these data were designed for research purposes only; therefore, participants' consent was not required. However, identification of participants was difficult due to the large and population-dwelling sample size.

Information about the diagnosis of hepatitis was based on health insurance claim data. However, as information about individuals without hepatitis was not available from the claim data, we used data from the sample cohort database for the group with individuals without hepatitis (Figure 1).

2.2 | Selection of participants

Patients who were newly diagnosed with chronic HBV infection (International Classification of Diseases, tenth edition [ICD-10]: B18.0 or B18.1), chronic HCV infection (ICD-10: B18.2) and co-infection (HBV/HCV) from 2005 to 2014 were selected as participants for this study. We excluded the following patients: (a) those who were <40 years of age and (b) those who had been diagnosed with PD (ICD-10: G20) or any Parkinson's-related diseases (secondary parkinsonism [ICD-10: G2], parkinsonism in diseases classified elsewhere [ICD-10: G22], other degenerative diseases of the basal ganglia [ICD-10: G23], and other extrapyramidal and movement disorders [ICD-10: G25]) before being diagnosed with HBV and HCV infections.

For the group without viral hepatitis, we used NHIS-NSC claims data from 2002 to 2013. The following patients were excluded: (a) those who were <40 years of age in 2003, (b) those with unknown information on age and sex in 2003, (c) those who had been diagnosed with acute or chronic HBV or HCV infection in 2002-2013, and (d) those who had been diagnosed with any PD or Parkinson's-related diseases in 2002.

2.3 | End point and comorbidity

The study end point at follow-up was PD diagnosis, death or censored (31 December 2015 for the group with viral hepatitis and 31 December 2013 for the group without viral hepatitis), whichever was first. The definition of PD was defined as the patients who were prescribed antiparkinsonism drugs among those diagnosed

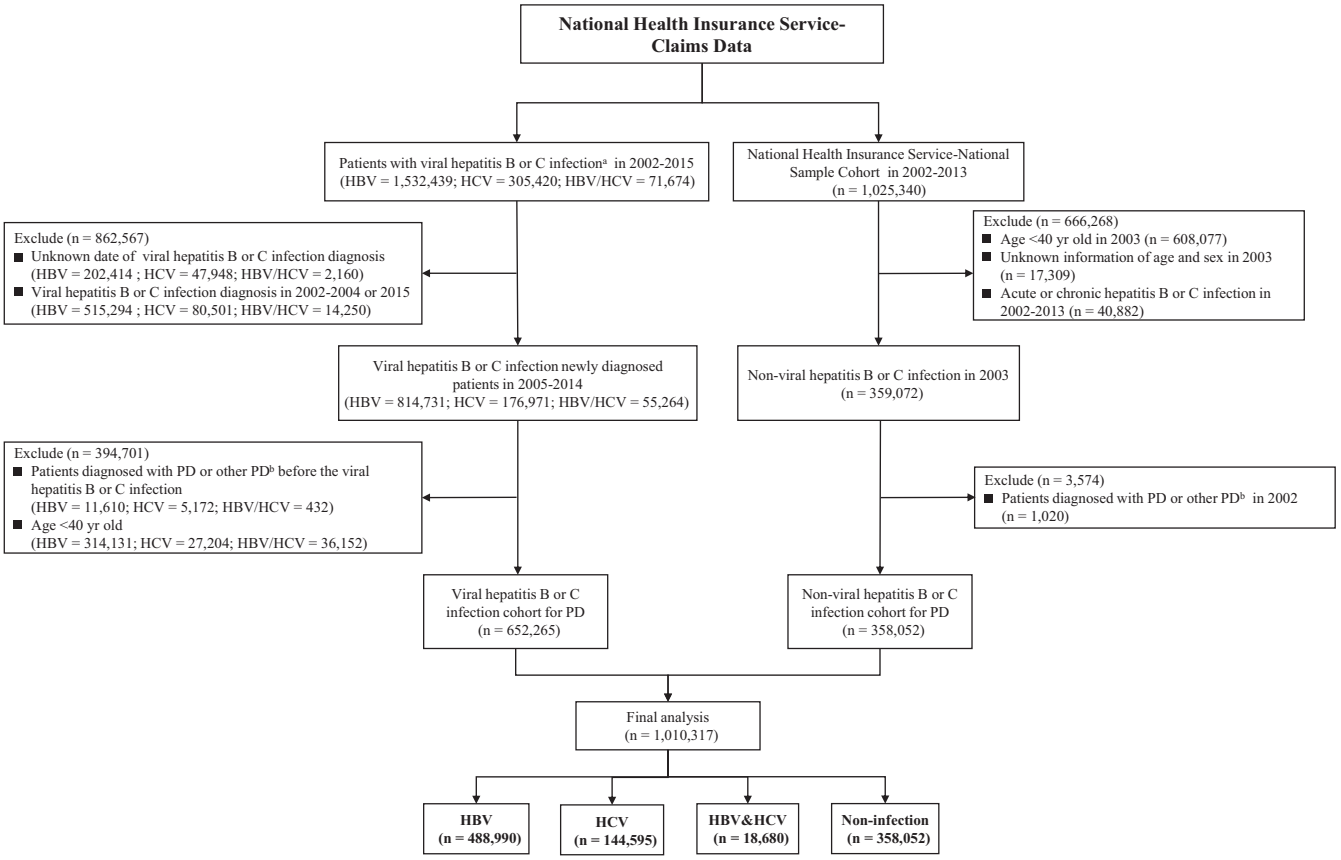

FIGURE 1 Flow chart of study subject selection. [a]HBV (ICD-10 : B18.0, B18.1), HCV (ICD-10 : B18.2), [b]Secondary parkinsonism (ICD-10 : G21), Parkinsonism in diseases classified elsewhere (ICD-10 : G22), Other degenerative diseases of basal ganglia (ICD-10 : G23) and Other extrapyramidal and movement disorders (ICD-10 : G25)

with ICD-10 code (G20). Comorbidities were defined with more than one admission or two outpatient visits between 2002 and the end point based on ICD-10 codes and comprised hyperlipidemia (E78), hypertension (I10-I15), ischaemic heart disease (I20-I25), epilepsy (G40), type 2 diabetes mellitus (E11), liver cancer (C22, C22.0 and C22.9), stroke (I60-I69), head injury (S00-S09), alcoholic liver disease (K70) and depressive disorder (F32). We included these comorbidities in the analysis because they are potential risk factors for PD.

2.4 | Statistical analyses

The incidence density of PD per 10 000 person-years was calculated as follows: The numerator was the number of newly diagnosed cases of PD during the observation period, and the denominator was the sum of the observation periods for all the individuals in the group. To assess the risk of PD, we estimated the cumulative incidence and hazard ratios for adjusted age, sex, comorbidity and death. The Fine and Gray competing risks regression models were used to formally analyse the association between risk factors and PD, considering that all-cause mortality was a competing risk.[12] The cumulative incidence rate in the HBV/HCV group was not calculated due to the small number of patients. Statistical significance was defined as P values < .05, and all statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.).

3 | RESULTS

The study cohort included 1 010 317 participants (358 052, participants with noninfections; 488 990, participants with HBV infections; 144 459, participants with HCV infections; and 18 680 participants with HCV/HBV infections) (Figure 1). Among total 1 010 317 participants, 4032 (0.4%) developed PD. The number of participants who developed PD was 1791 (0.5%) participants with noninfection; 1487 (0.3%) participants with HBV infections; 685 (0.5%) participants with HCV infections; and 69 (0.4%) participants with HBV/HCV infections. Mean ages at baseline at the time of viral infection diagnoses were 53.1, 57.1 and 55.7 years in the HBV, HCV and HBV/HCV groups, respectively. Average follow-up durations were 10.3, 6.1, 5.9 and 5.4 years in the noninfection, HBV, HCV and HBV/HCV groups, respectively. Overall, participants in the HCV group were older and everything had a higher prevalence of most of the selected comorbidities except the liver cancer, head injury and alcoholic liver

TABLE 1 Epidemiologic characteristics of the study participants by viral hepatitis infection in South Korea, 2005-2015

Variables	Noninfected (n = 358 052)		HBV (n = 488 990)		HCV (n = 144 595)		HBV/HCV (n = 18 680)		*P*-value*
	N	%	N	%	N	%	N	%	
Age at participants (year)									
40-49	153 972	43.0	208 128	42.6	41 663	28.8	5921	31.7	<.001
50-59	86 938	24.3	165 542	33.9	46 897	32.4	6593	35.3	
60-69	69 090	19.3	78 361	16.0	34 115	23.6	3989	21.4	
70-79	34 131	9.5	30 458	6.2	18 069	12.5	1889	10.1	
80+	13 921	3.9	6501	1.3	3851	2.7	288	1.5	
Sex									
Male	169 910	47.5	259 445	53.1	73 195	50.6	10 075	53.9	<.001
Female	188 142	52.5	229 545	46.9	71 400	49.4	8605	46.1	
Comorbidity[a]									
Hyperlipidemia	99 479	27.8	182 516	37.3	66 084	45.7	8344	44.7	<.001
Hypertension	156 705	43.8	195 350	39.9	73 290	50.7	8498	45.5	<.001
Ischaemic heart disease	44 940	12.6	60 807	12.4	28 367	19.6	2996	16.0	<.001
Epilepsy	6992	2.0	10 240	2.1	4760	3.3	493	2.6	<.001
Type 2 diabetes	66 636	18.6	103 650	21.2	41 095	28.4	5106	27.3	<.001
Liver cancer	1266	0.4	44 565	9.1	9735	6.7	2614	14.0	<.001
Stroke	46 286	12.9	51 628	10.6	22 960	15.9	2418	12.9	<.001
Head injury	46 360	12.9	88 381	18.1	28 418	19.7	3792	20.3	<.001
Alcoholic liver disease	12 738	3.6	46 338	9.5	18 285	12.6	2752	14.7	<.001
Depressive disorder	28 013	7.8	49 024	10.0	19 700	13.6	2339	12.5	<.001
Outcomes									
Parkinson's disease	1791	0.5	1487	0.3	685	0.5	69	0.4	<.001
Death	44 579	12.5	46 641	9.5	17 046	11.8	2248	12.0	
Censored (no PD, no death)	311 682	87.0	440 862	90.2	126 864	87.7	16 363	87.6	
Follow-up years									
Mean (SD)	10.2 (2.2)		6.1 (3.0)		5.9 (3.0)		5.4 (2.8)		
Median (Q1, Q3)	10.9 (10.9, 10.9)		6.3 (3.7, 8.7)		5.9 (3.4, 8.5)		5.4 (3.1, 7.8)		

[a]Comorbidities were defined with more than one admission or two outpatient visits as ICD 10th codes between 2002 and index date; hyperlipidemia(E78), hypertension(I10-I15), ischaemic heart disease(I20-I25), epilepsy(G40), type 2 diabetes mellitus(E11), liver cancer(C22, C22.0 and C22.9), stroke (I60-I69), head injury(S00-S09), alcoholic liver disease(K70) and depressive disorder(F32).

*P values were obtained using chi-square test.

disease than those in the other groups. All differences were statistically significant. Noticeable differences were also seen in the number of deaths during the follow-up period between the 4 groups: 44 579 (12.5%), participants with noninfections; 46 641 (9.5%), participants with HBV infections; 17 046 (11.8%), participants with HCV infections; and 2248 (12.0%), participants with HCV/HBV infections (Table 1).

The cumulative incidence rate of PD during the 11-year follow-up was 0.30% in the noninfection, 0.32% in the HBV and 0.53% in the HCV groups (Figure 2). The incidence density of PD per 10 000 person-years was the highest, at 8.0, in the HCV group, followed by 6.8 in the HBV/HCV group, 5.0 in the HBV group and 4.9 in the noninfection group. The incidence density of PD per 10 000 person-years increased with increasing age and highest in the 70-79 years with the exception of the HBV/HCV group. Especially, among HBV/HCV group, the incidence density of PD per 10 000 person-years was approximately 3 times higher in participants aged ≥80 years than in those aged 70-79 years. Moreover, the incidence density of PD per 10 000 person-years increased with the presence of comorbidities, including hypertension, ischaemic heart disease, epilepsy, type 2 diabetes mellitus, stroke and depressive disorder (Table S1).

Based on male patient in the noninfection group, the female patient had higher in HRs of PD than male patient in all 4 groups. In addition, based on the not diagnosed with comorbidities in noninfection group, the HRs of PD for those diagnosed with hypertension, ischaemic heart disease, epilepsy, stroke and depressive disorder were higher than those not diagnosed in the all groups. Patients with

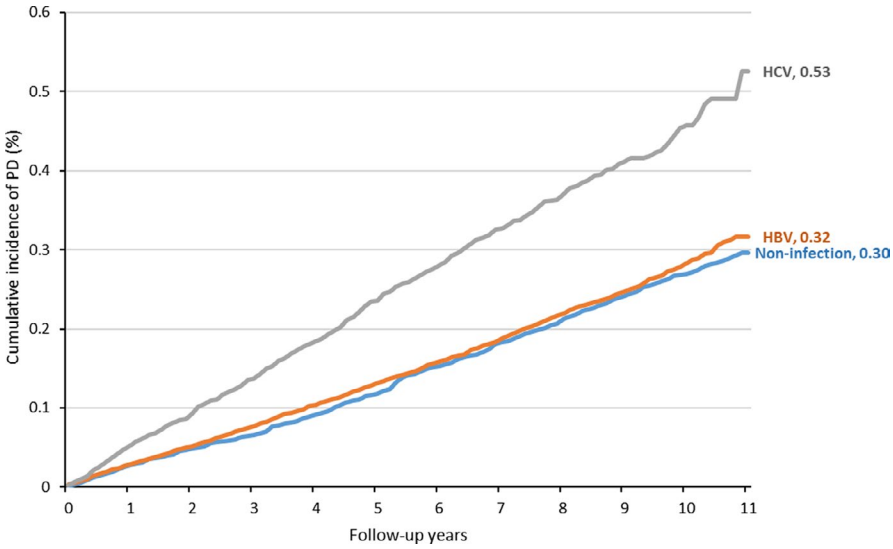

FIGURE 2 Adjusted (Age, sex, comorbidity and death) cumulative incidence of Parkinson's disease (PD) by viral hepatitis infection using Fine and Gray model, South Korea, 2005-2015

alcoholic liver diseases in the noninfection, HBV and HCV groups showed lower HRs than those without alcoholic liver diseases in the same groups (Table 2).

The adjusted HRs of PD for age, sex, comorbidities and death were calculated using multivariate competing risk analysis. HRs for PD in the nonadjusted model (model 1) were 1.06 (95% CI: 0.99-1.14), 1.71 (95% CI: 1.56-1.87) and 1.46 (95% CI: 1.15-1.86) in the HBV, HCV and HBV/HCV groups, respectively. When age and sex were included in the model, the HRs of PD went up to 1.40 (95% CI: 1.30-1.50) and 1.61 (95% CI: 1.26-2.04) in the HBV and HBV/HCV groups. However, after including age and sex in the model, HR of PD in the HCV group showed a slight decrease to 1.62 (95% CI: 1.48-1.77). When comorbidities were added to the model (model 3), only the HRs of HBV/HCV group increased to 1.66 (95% CI: 1.30-2.11). The final model (model 4) was adjusted for age, sex, comorbidities and death; the HRs were 1.25 (95% CI: 1.17-1.35), 1.39 (95% CI: 1.27-1.52) and 1.46 (95% CI: 1.14-1.85) in the HBV, HCV and HBV/HCV groups, respectively (Table 3).

4 | DISCUSSION

The epidemiology of PD and the association of PD with viral hepatitis infection need to be examined closely. In this study, we determined the incidence of PD and evaluated the association between PD and HCV/HBV infection by analysing extensive nationwide population-based data. We found that the incidence of PD per 10 000 person-years was the highest in the HCV (8.0), HBV/HCV (6.8) and HBV (5.0) infection groups, while the 11-year cumulative incidence of PD was the highest in the HCV, HBV and noninfection groups, in that order. The risk of PD increased proportionally with increasing age and with the presence of comorbidities, including hypertension, ischaemic heart disease, epilepsy, stroke and depressive disorder in all groups.

Hepatitis C virus and HBV, members of the Hepadnavirus family, have outer lipid envelopes and icosahedral nucleocapsid cores composed of protein.[13] HCV and HBV infections might lead to neurodegeneration in many ways such as by direct killing of the neurons through viral replication or by activating both innate and adaptive immune responses, leading to neuronal damage.[14] The innate immune response increases the expression of toll-like receptor (TLR) 2, TLR 5 and CD14 in the central nervous system of PD patients and activates natural killer cells, whereas the adaptive immune responses increase CD4 + T cells that then infiltrate the brain in PD patients.[14] Chronic neuroinflammation is also seen in the brains of PD patients.[15] In addition, HBV infection might induce severe inflammation through mediators such as interleukin-8 (IL-8), IL-29 and IL-22.17.[16] In a population-based cohort study in Taiwan, HCV infection was associated with PD as shown by an adjusted HR of 1.29 for age, sex and some comorbidities.[7] Another study also demonstrated a significant association between HCV and PD, as shown by an OR of 1.39 (95% CI: 1.07-1.80.11). Besides, a study showed that HCV induced the death of 60% of dopaminergic neurons in the midbrain neuron-glia co-culture system in rats, and the toxicity of HCV was similar to that of 1-methyl-4-phenylpyridinium; these features are but not caused by HBV.[6]

The annual incidence density of PD in our study was lower than that observed in Taiwan (85.88 in the noninfection, 91.16 in the HBV, 213.84 in the HCV and 110.19 in the HBV/HCV groups).[6,8] This difference might be attributed to various reasons. Firstly, the definition used for viral hepatitis infection in our study (only chronic hepatitis infection) differs from the one used in Taiwan (both acute and chronic hepatitis infections). Secondly, patients diagnosed with secondary PD and PD-related diseases till the end point were excluded from this study. Thirdly, using the Fine and Gray competing risk regression model analysis, we adjusted for all-cause mortality before the diagnosis of PD.

We found that the HBV, HCV and HBV/HCV groups showed increased risk of PD, which was higher in participants with HCV infection than in those with HBV infections. Unlike our results, a previous study suggested that the standardized rate ratio of PD was higher among patients with HBV infections (RR: 1.76, 95% CI: 1.28-2.37) than among those with HCV infections (RR: 1.51, 95%

TABLE 2 Hazard ratio for the development of Parkinson' disease by viral hepatitis infection using univariate competing risk[a] analysis

Variables	Noninfected	HBV	HCV	HBV/HCV
	Hazard ratio (95% confidence interval)			
Age at participants (year)				
40-49	1	1.55 (1.23-1.95)	2.05 (1.45-2.90)	2.5 (1.17-5.35)
50-59	3.69 (2.99-4.55)	4.01 (3.27-4.92)	4.87 (3.77-6.28)	3.74 (2.02-6.93)
60-69	13.59 (11.27-16.38)	13.31 (10.98-16.14)	14.35 (11.59-17.76)	14.25 (9.35-21.72)
70-79	20.36 (16.8-24.68)	27.39 (22.49-33.36)	28.64 (23.19-35.38)	21.82 (13.47-35.33)
80+	9.13 (6.98-11.93)	18.54 (13.68-25.14)	16.99 (11.59-24.9)	42.94 (18.91-97.50)
Sex				
Male	1	1.01 (0.90-1.12)	1.89 (1.66-2.15)	1.60 (1.16-2.22)
Female	1.43 (1.30-1.57)	1.47 (1.32-1.62)	1.96 (1.72-2.24)	1.62 (1.13-2.32)
Comorbidity[§]				
Hyperlipidemia				
No	1	0.89 (0.82-0.97)	1.54 (1.37-1.72)	1.26 (0.91-1.74)
Yes	0.90 (0.81-1.00)	1.08 (0.98-1.19)	1.51 (1.33-1.71)	1.30 (0.91-1.86)
Hypertension				
No	1	0.89 (0.8-0.99)	1.36 (1.17-1.59)	1.23 (0.82-1.83)
Yes	1.82 (1.66-2.00)	1.98 (1.79-2.18)	2.81 (2.50-3.16)	2.39 (1.76-3.24)
Ischaemic heart disease				
No	1	0.96 (0.89-1.04)	1.45 (1.31-1.61)	1.07 (0.79-1.45)
Yes	1.71 (1.52-1.92)	1.86 (1.65-2.10)	2.68 (2.33-3.09)	3.16 (2.14-4.66)
Epilepsy				
No	1	0.98 (0.91-1.05)	1.52 (1.39-1.67)	1.30 (1.01-1.66)
Yes	2.73 (2.22-3.37)	3.10 (2.54-3.79)	4.32 (3.37-5.55)	3.45 (1.43-8.32)
Type II diabetes				
No	1	0.87 (0.80-0.95)	1.38 (1.24-1.54)	1.13 (0.83-1.54)
Yes	1.06 (0.94-1.19)	1.44 (1.30-1.60)	2.05 (1.80-2.34)	1.81 (1.23-2.64)
Liver cancer				
No	1	1.07 (1.00-1.15)	1.63 (1.48-1.78)	1.37 (1.06-1.78)
Yes	0.34 (0.09-1.37)	0.39 (0.30-0.50)	0.96 (0.68-1.35)	1.03 (0.53-1.97)
Stroke				
No	1	0.90 (0.83-0.98)	1.36 (1.22-1.52)	1.20 (0.89-1.62)
Yes	2.68 (2.42-2.97)	3.49 (3.14-3.87)	4.55 (3.99-5.18)	3.99 (2.66-5.97)
Head injury				
No	1	0.94 (0.87-1.02)	1.48 (1.34-1.63)	1.21 (0.92-1.60)
Yes	0.82 (0.70-0.95)	1.10 (0.98-1.25)	1.75 (1.48-2.06)	1.54 (0.96-2.49)
Alcoholic liver disease				
No	1	0.99 (0.92-1.07)	1.60 (1.46-1.76)	1.36 (1.05-1.75)
Yes	0.54 (0.39-0.75)	0.86 (0.72-1.02)	1.17 (0.92-1.48)	0.95 (0.47-1.91)
Depressive disorder				
No	1	0.90 (0.84-0.98)	1.49 (1.35-1.66)	1.21 (0.92-1.61)
Yes	2.48 (2.20-2.80)	2.82 (2.52-3.15)	3.31 (2.84-3.86)	3.19 (2.03-5.02)

[a]All-cause mortality was the competing risk; competing risks regression model using the Fine and Gray method.

[§]Comorbidities were defined with more than one admission or two outpatient visits as ICD 10th codes between 2002 and index date; hyperlipidemia(E78), hypertension(I10-I15), ischaemic heart disease(I20-I25), epilepsy(G40), type 2 diabetes mellitus(E11), liver cancer(C22, C22.0 and C22.9), stroke (I60-I69), head injury(S00-S09), alcoholic liver disease(K70) and depressive disorder(F32).

TABLE 3 Hazard ratio for the development of Parkinson's disease by viral hepatitis infection using multivariate competing risk analysis[a]

Variables	Noninfected	HBV	HCV	HBV/HCV
Hazard ratio for Parkinson's disease (95% CI)				
Model 1 (Nonadjusted)	1	1.06 (0.99-1.14)	1.71 (1.56-1.87)	1.46 (1.15-1.86)
Model 2 (Age and sex adjusted)	1	1.40 (1.30-1.50)	1.62 (1.48-1.77)	1.61 (1.26-2.04)
Model 3 (Model 2 + comorbidities[b] adjusted)	1	1.40 (1.30-1.51)	1.59 (1.44-1.74)	1.66 (1.30-2.11)
Model 4 (Model 3 + death adjusted)	1	1.25 (1.17-1.35)	1.39 (1.27-1.52)	1.46 (1.14-1.85)

[a]All-cause mortality was considered as the competing risk; competing risks regression model using the Fine and Gray method.

[b]Comorbidities were defined with more than one admission or two outpatient visits as ICD 10th codes between 2002 and index date; hyperlipidemia(E78), hypertension(I10-I15), ischaemic heart disease(I20-I25), epilepsy(G40), type 2 diabetes mellitus(E11), liver cancer(C22, C22.0 and C22.9), stroke (I60-I69), head injury(S00-S09), alcoholic liver disease(K70) and depressive disorder(F32).

CI: 1.18-1.90).[5] Another study showed that the HRs adjusted for age, sex and comorbidities were 1.03 (95% CI: 0.85-1.25) for patients with HBV infections, 1.29 (95% CI: 1.06-1.56) for patients with HCV infections and 0.97 (95% CI: 0.67-1.40) for patients with HBV/HCV infections.[6,8] Also, the cross-sectional design study showed that the OR of PD were 0.79 (95% CI: 0.54-1.17) with HBsAg group and 1.95 (95% CI:1.02-3.72) with Anti-HCV group.[17] However, our study showed that the HRs were significantly higher HBV, HCV and HBV/HCV groups compared to noninfection groups, except for the crude HRs in HBV groups. Also, our study showed that most of the comorbidities, including hypertension, ischaemic heart disease, epilepsy, stroke and depressive disorder, were associated with an increased risk of PD in all groups. However, Tsai et al showed that in the HBV infection group, only hypertension was related to a high risk of PD, whereas in HCV group, ischaemic heart disease and head injury were found to be associated with an increased risk of PD.[7]

In addition, Tsai et al[8] showed no association between HBV infection and PD after adjusting for age, suggesting that further studies are required to clarify the relationship between HBV and PD. It is well-known that viruses such as HCV can invade the brain and lead to PD-related cell loss. The mechanism of the association between HCV infection and PD is described elsewhere.[6,7,18-21]

The findings that HCV infection, HBV infection, age, sex and comorbidities were associated with a high risk of PD have several implications. In osteoporosis, predictive models, such as the Garvan Fracture Risk Calculators[22] and the Fracture Risk Assessment Tool2, have been used for predicting fractures. Our finding suggests that a predictive model can be developed for predicting PD based on HCV infection, HBV infection, age, sex and comorbidities. Secondly, the finding implies that PD is partially preventable, because HBV infection, HCV infection and comorbidities are potentially modifiable factors. Thirdly, since HCV and HBV infections were found to increase the risk of PD, we emphasize that patients with viral infections should be considered for early diagnosis and treatment of PD.

The strength of this study was that the results were derived from a well-characterized cohort, with long-term follow-up and large sample size. Moreover, by using competing risk analysis[23] for analysing the association between viral hepatitis infection and PD, we were able to make refined predictions of an individual's risk for PD. However, there are some limitations. The first limitation is the use of the NHIS-NSC cohort database as the source of information for the group without hepatitis. However, Korean NHI claims data covers almost the entire Korean population (98.5%). In addition, the NHIS-NSC cohort database is representative because it was sampled by NHIS based on age, sex, and income level and includes data on 1 020 340 individuals, comprising approximately 2.2% of the population registered with NHIS in 2002. Secondly, this study participant was not ascertained by clinical assessment but by ICD-10 codes. The HBV and HCV diagnoses were defined as those who were treated for these conditions according to the ICD 10 codes. The viral hepatitis group only included individuals with chronic hepatitis and did not include those treated for acute hepatitis. In addition, individuals with viral hepatitis who did not seek health care, or who were not tested for viral hepatitis were not included. Furthermore, individuals diagnosed with PD may have had a greater number of opportunities to be diagnosed with viral hepatitis due to a greater number of hospital visits than individuals without viral hepatitis. However, the possibility of this bias was prevented by excluding individuals diagnosed with viral hepatitis after a diagnosis of PD. There is no information about HBsAg and anti-HCV test results in the NHIS-NSC cohort database. Hence, we could not consider or confirm these test results when defining the noninfection group. To complement this, participants who were diagnosed or treated at least once with acute or chronic viral hepatitis ICD-10 codes in the NHIS-NSC cohort database from 2002 to 2013 were excluded from the noninfection group. As a result, the noninfection group included participants who had never been diagnosed with, or treated for, acute or chronic hepatitis virus for 12 years, thereby compensating for the lack of HBsAg or anti-HCV test results. The last limitation is that the study did not include data on antiviral treatment, potential risk factors for PD such as family history of PD, cigarette smoking, alcohol, physiological factors (such as body mass index, fasting blood sugar and blood pressure) and drug abuse. Further studies should be conducted in other settings to further evaluate the association between HBV and HCV infections with PD. In conclusion, this study demonstrates that HCV and HBV infections are independent risk

factors for PD development. Our findings also indicate that comorbidities and advancing age increase the risk of PD in patients with viral hepatitis infections. Taken together, our findings suggest that elderly patients with HBV or HCV infections who are diagnosed with HCV or HBV infections should be monitored for signs of PD so that early intervention and accurate treatment can be provided to minimize the development and consequences of PD.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

In this project, all jobs were done under the supervision of Prof. Moran Ki. Hwa Young Choi contributed to the study design, analysed the data, wrote the first draft of the manuscript and reviewed the manuscript. Ha Thi Mai wrote the first draft of manuscript. Dr Kyung-Ah Kim and Dr Hyunsoon Cho, together with Dr Moran Ki, revised the manuscript in terms of organization and writing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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