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Impact of nucleos(t)ide analogue therapy on the incidence of Alzheimer's disease in patients with chronic hepatitis B virus infection

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Abstract

Background Long-term therapy with nucleos(t)ide analogs (NUCs) is inevitable for chronic hepatitis B (CHB) patients. However, how NUC therapy on the developing Alzheimer's disease (AD) in these patients remains controversial.

Methods This retrospective cohort study used the Korean National Health Insurance Service claims database from January 1, 2013, to December 31, 2013, treatment naïve CHB patients and those without previously diagnosed with AD. Participants were followed from the index date until either the diagnosis of AD or the study's conclusion on December 31, 2021. The primary outcome was the incidence of AD, compared between the group with initiated NUC therapy ($n=18,365$) at cohort entry and the group without NUC therapy ($n=212,820$).

Results During the study, 416 patients were diagnosed with AD. After propensity-score matching (18,365 pairs), the 5- to 7-year follow-up showed a significantly lower hazard ratio (HR) in the NUC-treated group compared to the untreated group (HR 0.31–0.40), with HRs remaining constant over time. Subgroup analysis showed more pronounced benefits of NUC therapy in patients under 65 years (HRs: 0.22 vs. 1.23; $P<0.05$) and those without dyslipidemia (HRs: 0.14 vs. 1.09; $P<0.05$). Protective effects were also observed across subgroups with hypertension, chronic kidney disease, heart disease, and a history of brain trauma, consistent with AD risk factor trends.

Conclusions Our study analyses suggest that NUC therapy appears to have a protective effect against the development of AD in patients with CHB.

Keywords Chronic hepatitis B virus, Nucleos(t)ide analogs, Alzheimer's disease, Incidence

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Introduction

Chronic hepatitis B virus infection (CHB) has been a leading cause of cirrhosis and liver cancer [1, 2]. Nucleos(t)ide analogs (NUC) are used to suppress chronic inflammation caused by viral replication and to prevent the progression of liver disease, serving as the standard of care administered worldwide [3–5]. Although the effectiveness and utility of NUC therapy are well-established, current NUC treatment is not designed to be a short-term cure but rather to suppress viral replication for the duration of use, making prolonged NUC therapy inevitable. As a result, the majority of patients are on long-term NUC therapy, even decades of years after initiation [3, 6–8].

Long-term NUC use in patients with CHB has been associated with toxicities such as myopathy, neuropathy, and nephropathy, which are mechanistically linked to the cumulative mitochondrial damage caused by NUC therapy [9–13]. In general, neurodegenerative disease (ND) is a representative disease associated with the accumulation of mitochondrial damage over time [14, 15]. However, there has been little research on the impact of NUC therapy on the development of ND in patients with CHB.

Alzheimer's disease (AD), the most common ND, has been linked to chronic liver disease in several studies, potentially contributing to neuroinflammation over time [16]. Mechanistic links between chronic hepatitis virus and AD-related cellular pathways involve disruption in essential cellular processes, leading to protein mislocalization and inflammatory responses, including leukocytes activation, particularly of microglial cells [17, 18]. In line with this mechanism, CHB may contribute to AD development [17, 19, 20]. Additionally, viral suppression through NUC therapy may exert a protective effect against AD by reducing inflammatory cytokines and mitigating neuroinflammation associated with chronic hepatitis [21, 22]. However, while NUC use and maintenance theoretically offer protection against AD by suppressing the inflammatory process, prolonged NUC therapy may induce mitochondrial damage, potentially accelerating the onset of AD.

Given this background, we evaluated whether NUC in CHB reduce AD incidence and how long-term NUC use impacts AD development by comparing AD rates in CHB patients with and without NUC therapy using a national data set from a CHB-endemic area.

Materials and methods

Data source

This study examined the risk of AD in patients with CHB infection based on the NUC administration, using a nationwide population-based cohort from Republic of Korea [23]. The cohort was established using health insurance claims data from the Korea National Health Insurance Service (NHIS), which covers approximately 97% of Korean residents-based insurance. The NHIS maintains a comprehensive health database, including diagnoses, treatments, procedures, and prescriptions [24, 25]. Patient demographic information, medical treatment records, and detailed diagnoses coded using the Korean Standard Classification of Disease Version 5 (a modification of ICD-10) were collected for all individuals between January 1, 2013, and December 31, 2013. This study was approved by the Institutional Review Board of Hanyang University Guri Hospital, with all methods performed according to relevant guidelines and regulations (IRB No. 2023-04-039). The retrospective study was performed in accordance with the Declarations of Helsinki and written informed consent was waived by the Institutional Review Board.

Study population

The study population comprised patients aged 30 to 70 years with CHB from January 1, 2013, to December 31, 2013, who had no prior experience with NUC therapy and were not diagnosed with AD before cohort entry ($n = 273{,}503$, Fig. 1). All patients had an International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) code of B181 or B180, indicating a diagnosis of CHB. AD was defined according to previous studies as individuals with a primary or subsidiary diagnosis of AD (ICD-10 code G30) [26, 27]. To specifically evaluate the effects of viral suppression and NUC toxicity from a neurodegenerative disease perspective, vascular or mixed-cause dementias were excluded from this analysis as they were not relevant [19, 28]. We excluded patients identified from the period before to one year after cohort entry, the following exclusions were made: 2,434 patients with chronic hepatitis C virus infections, 104 patients with human immunodeficiency virus infection, 3,736 patients with acute viral hepatitis, 1,655 patients who had undergone liver transplantation, 447 patients who had undergone stem cell transplantation, 10,065 patients previously diagnosed with hepatocellular carcinoma, 11,290 patients with a previous diagnosis of non-hepatic primary cancer, 4,008 patients with a history of stroke, and 1,545 patients who died during the cohort entry period. After these exclusions, a total of 238,219 patients were included in the study.

In addition, patients prescribed NUC for CHB and who adhered to the treatment regimen for more than 80% of the duration were categorized as the treated group, while those with an adherence rate below 80% were excluded ($n = 7{,}034$). Conversely, patients who were not prescribed NUC at all were classified as the untreated group. Ultimately, our cohort comprised 18,365 patients (the treated group) who received newly initiated NUC therapy and 212,820 patients (the untreated group) who did not

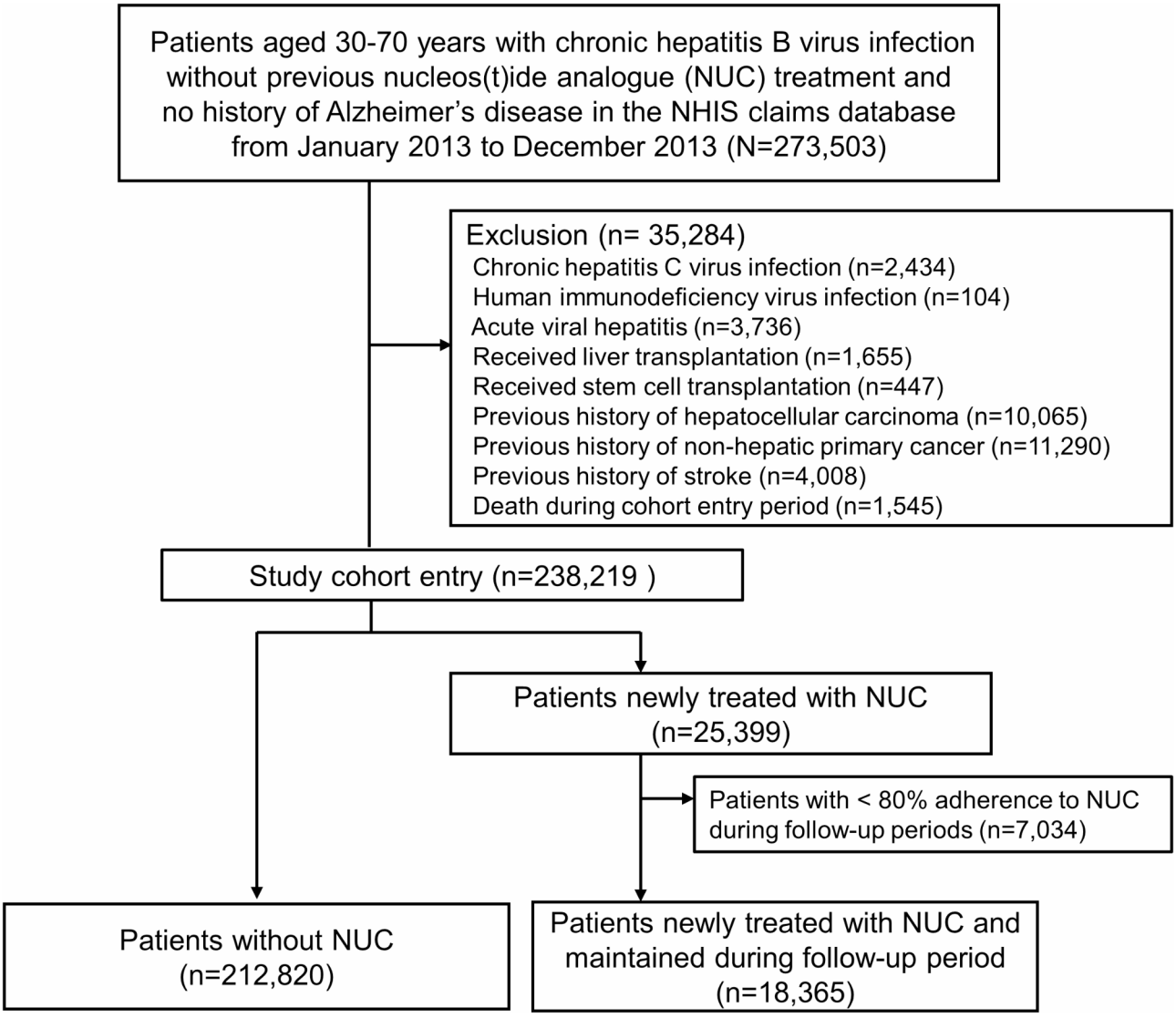

Fig. 1 Flowchart of the study design

receive NUC. Patients in the untreated group who initiated NUC therapy or those in the treated group with NUC adherence < 80% were excluded from the analysis. Baseline data for the treated group were obtained at the initiation of NUC therapy, and for the untreated group, data were collected from the first claim date for CHB during 2013. Both groups were analyzed for the incidence of AD following a 6-month washout period after cohort entry. We collected claims data encompassing age, sex, socioeconomic status, level of healthcare, cirrhosis, and preexisting comorbidities such as diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, congestive heart failure, ischemic heart disease, and traumatic brain injury. Participants were followed from the index date until either the diagnosis of AD or the study's conclusion on December 31, 2021. Individuals were censored at the date of death. The detailed operational definitions used in this study are summarized in Supplementary Table 1.

Study outcome

The primary outcome of this study was the incidence of AD during the follow-up period. Only those whose AD occurred more than 1 year after cohort entry were analyzed. We defined newly diagnosed cases of AD as individuals who were newly diagnosed with AD. If there were several claims with AD codes (G30), the first time AD occurred was considered the time of AD diagnosis. The secondary objective was to identify the risk factors associated with AD in patients with CHB with or without NUC therapy.

Statistical analysis

All patients who met the eligibility criteria at baseline were included in the analyses. Categorical and continuous variables were compared using the Chi- square test and t- test respectively. The Cox proportional hazard model was used to compare the outcomes between the groups. We calculated the crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Propensity score- matching analysis was performed to reduce the effect of selection bias and potential confounding factors between the treated and non-treated groups. Propensity scores were derived using the following variables: age, sex, socioeconomic status, level of health care, and preexisting comorbidities such as diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, congestive heart failure, ischemic heart disease, traumatic brain injury, and cirrhosis. For propensity score matching, an SAS matching macro, "%OneToManyMTCH," was used for this caliper matching of nearest-neighbor approach for the first four to eight digits of propensity scores. The multivariable analysis included the following variables: age, sex, socioeconomic status, level of health care, and preexisting comorbidities such as diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, congestive heart failure, ischemic heart disease, traumatic brain injury, and cirrhosis. Since occurrence of death can lead to informative censoring in the assessment of the risk of AD, competing risk analysis was performed using Fine and Gray's proportional sub- distribution hazard model [29, 30]. The cumulative incidence risk of AD at 2, 3, 4, 5, 6, and 7 years following NUC therapy. In addition, time-dependent effects were evaluated based on Schoenfeld's residuals, and cubic spline functions were introduced in the model [31–33]. Kaplan–Meier method and compared using the log-rank test between treated and untreated groups both before and after PS matching. All statistical analyses were performed using SAS Enterprise Guide 7.1(SAS Institute Inc., Cary, NC) and R, version 4.3.1 (http://cran.rproject.org/). All reported p values are two- sided, and p values < 0.05 were considered statistically significant.

Results

Baseline characteristics of the entire cohort

The baseline characteristics of the study cohort are presented in Table 1. The median follow-up duration for the

Table 1 Baseline characteristics of patients before and after propensity score matching

Variable	Before matching, No. (%)			After Matching, No. (%)		
	Untreated group	Treated group*	*P* value	Untreated group	Treated group*	*P* value
Number of patients	212,820	18,365		18,365	18,365	
Age, mean (SD), years	49.45 (10.36)	47.82 (9.53)		48.00 (9.70)	47.82 (9.53)	
Age group, years			< 0.001			0.9995
30–40, n (%)	48,238 (22.67)	4,534 (24.69)		4,532 (24.68)	4,534 (24.69)	
41–50, n (%)	61,017 (28.67)	6,242 (33.99)		6,233 (33.94)	6,242 (33.99)	
51–60, n (%)	69,253 (32.54)	5,786 (31.51)		5,794 (31.55)	5,786 (31.51)	
60–70, n (%)	34,312 (16.12)	1,803 (9.82)		1,806 (9.83)	1,803 (9.87)	
Male sex, n (%)	112,116 (52.68)	11,158 (60.76)	< 0.001	11,161 (60.77)	11,158 (60.76)	0.9744
Socioeconomic status, n (%)			< 0.001			0.9960
Household income > 75, n (%)	82,882 (38.94)	7,279 (39.64)		7,271 (39.59)	7,279 (39.64)	
Household income 25–75, n (%)	80,210 (37.69)	7,114 (38.74)		7,116 (38.75)	7,114 (38.74)	
Household income < 25, n (%)	43,680 (20.52)	3,475 (18.92)		3,487 (18.99)	3,475 (18.92)	
Unknown	6,048 (2.84)	497 (2.71)		491 (2.67)	497 (2.71)	
Level of health care, n (%)			< 0.001			0.9530
Tertiary, n (%)	55,088 (25.88)	6,688 (36.42)		6,670 (36.32)	6,688 (36.42)	
Secondary, n (%)	101,416 (47.65)	8,604 (46.85)		8,601 (46.83)	8,604 (46.85)	
Primary, n (%)	56,316 (26.46)	3,073 (16.73)		3,094 (16.85)	3,073 (16.73)	
Cirrhosis, n (%)	15,249 (7.17)	5,586 (30.42)	< 0.001	5,577 (30.37)	5,586 (30.42)	0.9187
Preexisting comorbidity						
Diabetes mellitus, n (%)	51,679 (24.28)	3,447 (18.77)	< 0.001	3,436 (18.71)	3,447 (18.77)	0.8831
Hypertension, n (%)	60,415 (38.39)	4,018 (21.88)	< 0.001	3,996 (21.76)	4,018 (21.88)	0.7811
Dyslipidemia, n (%)	103,031 (48.41)	7,644 (41.62)	< 0.001	7,646 (41.63)	7,644 (41.62)	0.9831
Chronic kidney disease, n (%)	2,754 (1.29)	103 (0.56)	< 0.001	92 (0.5)	103 (0.56)	0.4296
Congestive heart failure, n (%)	2,936 (1.38)	157 (0.85)	< 0.001	146 (0.79)	157 (0.85)	0.5257
Ischemic heart disease, n (%)	14,449 (6.79)	840 (4.57)	< 0.001	812 (4.42)	840 (4.57)	0.4809
Traumatic brain injury, n (%)	2,092 (0.98)	136 (0.74)	0.0013	116 (0.63)	136 (0.74)	0.2061

Abbreviations: SD, standard deviation

*The type of newly initiated nucleos(t)ide analogue therapy was as follows: tenofovir disoproxil 66.6%, entecavir 22.3%, and other NUCs 11.2%

study population was 7.8 years. NUC therapy was initiated with 18,365 patients. Patients receiving NUC therapy tended to be younger (47.82 ± 9.53 vs. 49.45 ± 10.36; $P < 0.001$) and predominantly male (60.76% vs. 52.68%; $P < 0.001$), with a lower prevalence of comorbidities but a higher prevalence of cirrhosis 30.42% vs. 7.17%; $P < 0.001$) compared to patients without NUC therapy group. After propensity score matching, the baseline characteristics of the two groups did not significantly differ for the matching covariates, indicating good balance between the groups. During the study period, a total of 416 patients were diagnosed with AD. In the group NUC therapy, the incidence density was 0.07 per 100,000 person-years (PYs), while it was 0.03 per 100,000 PYs in the group not receiving NUC (Supplementary Table 2). In the propensity score-matched cohort, the incidence density of AD remained higher in the group not NUC (0.06 per 100,000 PYs, incidence rate 0.47 per 1,000 person) compared to the group receiving NUC (0.03 per 100,000 PYs, incidence rate 0.23 per 1,000 person). When compared with the known incidence rate in the general population aged 65–69 years (0.41 per 1,000 persons), the untreated group showed a slightly higher tendency, while the treated group demonstrated a lower tendency [26].

Risk of Alzheimer's disease in patients with chronic hepatitis B virus infection

We calculated the cumulative incidence and hazard ratios for AD at 2, 3, 4, 5, 6, and 7 years of follow-up (Table 2). In the unadjusted competing risk model, the NUC-treated group consistently showed lower hazard ratios across all follow-up periods than the untreated group. In the fully adjusted competing risk model, 5 years of follow-up (HR 0.31; 95% CI 0.14–1.00) showed statistical significance and continued to 7 years of follow-up (HR 0.40; 95% CI 0.22–0.73). In the propensity score-matched cohort of 18,365 pairs, the cumulative incidences in the 5- to 7-year follow-up groups showed a statistically significant lower HR in the NUC-treated group compared to the untreated group. (Fig. 2) In the Kaplan-Meier analysis, the NUC-treated group showed a statistically significant lower incidence of AD compared to the untreated group ($P = 0.014$). Additionally, the estimated hazard functions indicated that the hazard ratio remained constant over time. (Fig. 3)

Subgroup analysis of risk factors for Alzheimer's disease in patients with chronic hepatitis B virus infection

We conducted a subgroup analysis using the propensity score-matched pairs (Table 3). The NUC-treated group showed statistically significant lower HRs in females and in patients without cirrhosis, hypertension, dyslipidemia, chronic kidney disease, congestive heart failure, ischemic heart disease, or traumatic brain injury (all P values < 0.05). Subgroup analysis demonstrated more pronounced benefits of NUC therapy in patients aged < 65 years (HRs for age < 65 years and ≥ 65 years: 0.22 vs. 1.23; P for interaction = 0.010) and in those without dyslipidemia (HRs for without dyslipidemia and with dyslipidemia: 0.14 vs. 1.09; P for interaction = 0.006). The Kaplan-Meier curves for representative groups (age, sex, and cirrhosis) showed consistent results (Supplementary Fig. 1).

Table 2 Cumulative incidence and hazard ratio of Alzheimer's disease between groups

			Simple competing risk model		Multiple competing risk model**		Propensity score-matched model	
Year	**NUC Treatment group**	**Cumulative Incidence (95% CI)**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
2	NUC (-)	0.0002 (0.0002–0.0003)	1.00		1.00		1.00	
	NUC (+)	0.0001 (0 – 0.0004)	0.46 (0.11–1.91)	0.286	0.51 (0.12–2.05)	0.339	0.40 (0.08–2.06)	0.273
3	NUC (-)	0.0004 (0.0003–0.0005)	1.00		1.00		1.00	
	NUC (+)	0.0002 (0–0.0005)	0.44 (0.14–1.38)	0.156	0.55 (0.18–1.69)	0.294	0.43 (0.11–1.66)	0.220
4	NUC (-)	0.0006 (0.0005–0.0007)	1.00		1.00		1.00	
	NUC (+)	0.0002 (0.0001–0.0005)	0.37 (0.14-1.00)	0.051	0.51 (0.19–1.39)	0.187	0.36 (0.12–1.14)	0.083
5	NUC (-)	0.0009 (0.0008–0.0010)	1.00		1.00		1.00	
	NUC (+)	0.0003 (0.0001–0.0006)	0.31 (0.13–0.75)	0.009	0.41 (0.17-1.00)	0.049	0.33 (0.12–0.92)	0.033
6	NUC (-)	0.0012 (0.0011–0.0013)	1.00		1.00		1.00	
	NUC (+)	0.0005 (0.0002–0.0009)	0.41 (0.21–0.80)	0.009	0.55 (0.28–1.07)	0.079	0.41 (0.19–0.89)	0.024
7	NUC (-)	0.0015 (0.0013–0.0017)	1.00		1.00		1.00	
	NUC (+)	0.0006 (0.0003–0.0011)	0.40 (0.22–0.73)	0.003	0.54 (0.29–0.99)	0.045	0.38 (0.19–0.76)	0.006

Abbreviations: HR, hazard ratio; CI, confidence interval, NUC, nucleos(t)ide analogue

** Adjusted: age, sex, Socioeconomic status, cirrhosis, level of health care, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, congestive heart failure, ischemic heart disease, and traumatic brain injury

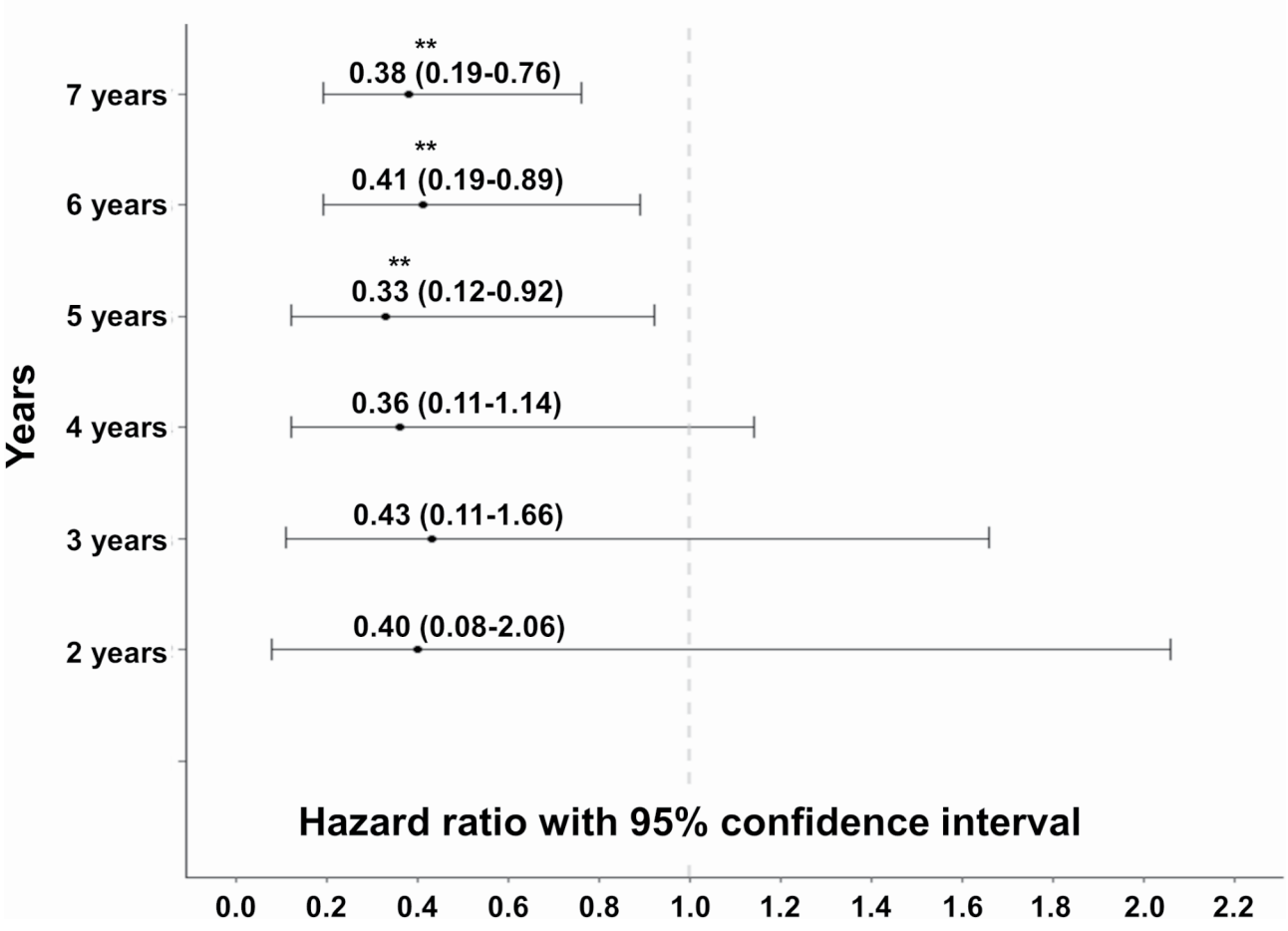

Fig. 2 Risk of Alzheimer's disease over time

Discussion

There have been reports suggesting a link between chronic hepatitis and the development of AD, which indicate etiology-specific treatment to suppress hepatitis could potentially reduce the incidence of AD [17, 20]. CHB infection, one of the leading causes of chronic hepatitis, has been treated with NUCs as the standard therapy for viral suppression, which has proven effective in preventing liver disease progression and reducing hepatocellular carcinoma [3]. From the perspective of ND prevention, the suppressing viral activity could potentially reduce the risk of AD associated with neuroinflammation [20, 34]. However, the use of NUCs does not aim for viral eradication, and maintenance therapy is required for several years after initiation [3, 7] Theoretically, prolonged NUC use could be associated with cumulative mitochondrial damage and may contribute to the promotion of ND [6, 12, 14, 35] Despite the widespread, long-term use of NUCs, there has been no research evaluating the impact of NUC therapy on the incidence of AD in CHB patients.

Previous studies suggested that hepatotropic viral infections are potential triggers for AD, inducing chronic neuroinflammation proposed as the underlying mechanism [17, 20] Among the studies concerning the risk of AD in chronic viral hepatitis, chronic hepatitis C has been associated with an increased risk of dementia, while viral eradication has been linked to a reduced risk of AD [34, 36] These results suggests that the increased AD risk due to chronic viral hepatitis might be reduced through effective viral suppression. Unfortunately, there has been no research exploring AD risk by suppressing CHB. One cross-sectional analysis of largest nationwide data, the odds ratio for presence of AD in CHB patients was not statistically significantly higher than in the control group. However, this study did not evaluate neither incidence of AD nor the influence of NUC therapy [37].

A key difference between the treatment of CHB and chronic hepatitis C lies two aspects: the selection of patients for treatment initiation and the need for continuous therapy. Unlike chronic hepatitis C, NUC therapy for CHB necessitates continuous use, and CHB treatment initiation criteria incorporate inflammation status (e.g., serum ALT levels and occasionally histologic findings),

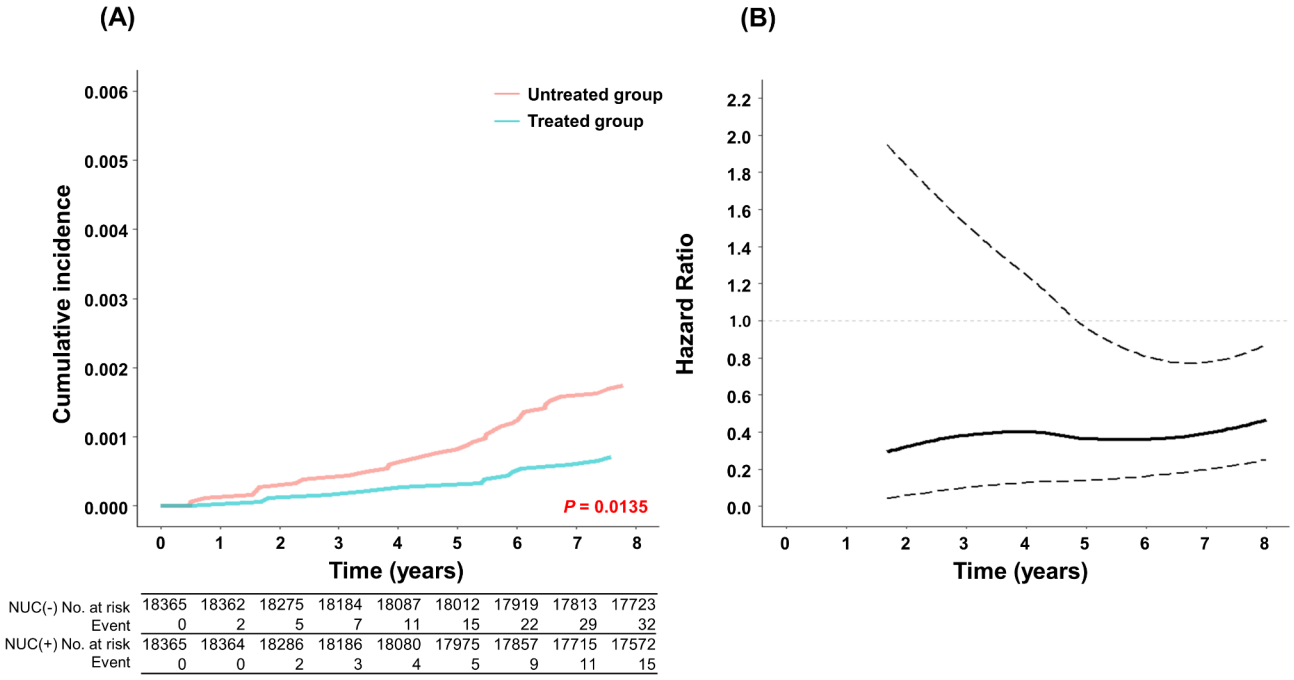

Fig. 3 Comparison of Alzheimer's disease event rates between the NUC-treated and untreated groups using (**A**) Kaplan-Meier analysis and (**B**) an estimate of the hazard function ratio (with pointwise bands showing 95% confidence intervals)
Abbreviations: NUC, nucleos(t)ide analogue

in contrast to CHC treatment. Under these backgrounds, it is crucial to determine whether effective viral suppression through NUCs reduces the risk of AD or if the cumulative mitochondrial toxicity from long-term NUC use increases AD risk. Understanding which of these factors exerts a dominant clinical effect in long-term NUC users is crucial. Our study results show that the NUC-treated group shows lower risk of AD compared to the untreated group, regardless of the duration of time-period. Although mechanistically, there have been suggestions of a potential link between cumulative NUC toxicity and increased AD risk [9–11], our study found that NUC use was associated with a proportionally lower risk of AD. Whether the protective effect of NUC therapy is consistent with other types of ND in CHB patients remains to be clarified. In terms of selecting patients for NUC initiation, differences in chronic inflammatory status between the treated and untreated groups may influence the degree of AD incidence. In patients with chronic hepatitis C, treatment eligibility is determined by viral replication status, with all individuals without contraindications being eligible for therapy. In contrast, for CHB, treatment is initiated based on the confirmation of chronic hepatitis, typically indicated by elevated serum ALT levels [3, 38]. In the untreated group, it is possible that lower baseline viral activity and inflammatory status may account for the lack of association with AD incidence. However, even in cases where clinical indications for initiating NUC therapy are not met, chronic inflammation and an increased risk of liver-related outcomes have been reported [3, 39, 40]. In other words, there are clinical scenarios where CHB patients do not meet the NUC indications despite having conditions such as fluctuating ALT levels during the immune active phase or persistent chronic inflammation that exceeds normal ALT levels but does not reach the threshold for treatment initiation. In contrast, in the NUC-treated group, viral activity is controlled, and chronic hepatitis may be resolved. Consequently, it is plausible that the relative protective effect against AD became more prominent over time in the NUC-treated group. However, the underlying detailed mechanisms by which NUC use reduces AD incidence in patient with CHB remain to be elucidated.

In the general population, the incidence of AD is known to be influenced by various risk factors [19]. To determine whether these well-known AD risk factors are also associated with CHB patients, we conducted additional subgroup analyses using propensity score-matched pairs, applying competing risk analysis and Kaplan-Meier analysis. First, in the case of advanced age, the use of NUCs in the CHB group age ≥ 65 years did not show the reduction in AD risk as observed in patients with age < 65 years. This may be due to the predominant effect of age itself on AD development or the accumulation of various medical and environmental risk factors that increase with age [28, 41, 42]. In contrast, the suppression of viral replication in younger CHB patients may more effectively

Table 3 Subgroup analysis of the hazard ratio of Alzheimer's disease between treated- and untreated-group

Subgroup		Propensity score-matched model				
		HR*	95% CI		*P*-value	*P*-value of interaction
sex	**Male**	0.50	0.19	1.33	0.1656	ref.
	Female	0.45	0.21	0.99	0.0463	0.8679
Age	**< 65 years**	0.22	0.08	0.57	0.0019	ref.
	≥ 65 years	1.23	0.50	3.02	0.6561	0.010
Socioeconomic status	**Income > 75%**	0.62	0.20	1.91	0.4082	ref.
	Income 25–75%	0.40	0.16	1.03	0.0577	0.5514
	Income < 25%	0.45	0.14	1.45	0.1785	0.6842
Level of health care	**Tertiary hospital**	0.57	0.24	1.36	0.2039	ref.
	Secondary hospital	0.40	0.16	1.03	0.0576	0.5890
	Primary hospital	0.34	0.04	3.23	0.3443	0.6689
Cirrhosis	**No**	0.31	0.12	0.85	0.0232	ref.
	Yes	0.62	0.28	1.37	0.2410	0.2896
Diabetes mellitus	**No**	0.50	0.24	1.03	0.0607	ref.
	Yes	0.40	0.13	1.27	0.1193	0.7426
Hypertension	**No**	0.28	0.10	0.75	0.0113	ref.
	Yes	0.71	0.32	1.60	0.4073	0.1516
Dyslipidemia	**No**	0.14	0.04	0.48	0.0016	ref.
	Yes	1.09	0.48	2.47	0.8350	0.0063
Chronic kidney disease	**No**	0.47	0.25	0.87	0.0155	ref.
	Yes	Inf.	Inf.	Inf.	Inf.	Inf.
Congestive heart failure	**No**	0.44	0.23	0.82	0.0099	ref.
	Yes	Inf.	Inf.	Inf.	Inf.	Inf.
Ischemic heart disease	**No**	0.41	0.21	0.81	0.0103	ref.
	Yes	0.97	0.20	4.78	0.9654	0.3388
Traumatic brain injury	**No**	0.47	0.25	0.87	0.0155	ref.
	Yes	Inf.	Inf.	Inf.	Inf.	Inf.

Abbreviations: HR, hazard ratio; CI, confidence interval, NUC, nucleos(t)ide analogue; ref, reference; inf, infinite

* The hazard ratio (HR) represents the risk in the NUC-treated group compared to the untreated group

reduce the risk of AD. Second, it is well-known that females in the general population have a higher risk of AD compared to males [19]. In CHB patients, females showed a more pronounced reduction in AD risk with NUC use. Whether this is due to the suppression of neuroinflammation caused by viral replication or differences in susceptibility to NUC toxicity remains unclear [43, 44]. Third, NUC therapy appeared to provide a more pronounced protective effect against AD in CHB patients who had not yet developed cirrhosis. Mechanistically, the risk of AD is more likely linked to hepatic active inflammation rather than the presence of cirrhosis itself [17, 22]. Although no statistically significant interaction was observed between the cirrhosis and non-cirrhosis groups, the protective effect of NUCs against AD was more pronounced in the non-cirrhosis group, despite NUCs being expected to reduce chronic inflammation caused by viral activity in both groups. This may reflect the clinical challenge of differentiating cognitive impairment in cirrhosis from coexisting ND, including AD [45, 46]. Further analysis is needed to determine whether NUCs have a protective effect or contribute to AD incidence through toxicity in cirrhotic versus non-cirrhotic patients. Fourth, although the interaction was not statistically significant except for age and dyslipidemia, the protective effect of NUCs against AD was maintained across the subgroups including hypertension, chronic kidney disease, heart disease, and a history of brain trauma. This aligns with the general trend of AD risk factors reported in the literature [19, 27, 28]. In summary of the subgroup analyses, NUC therapy generally showed protective effects across all subgroups, with the effect being more pronounced in CHB patients under 65 years of age and those without dyslipidemia. However, it remains unclear whether the management of medical risk factors through medication influences the response to NUC therapy in terms of AD risk in CHB patients, and further study is needed.

Strength and limitations

To our knowledge, this is one of the first studies to compare the relationship between NUC use and AD incidence in CHB patients using a nationally representative cohort from a CHB-endemic area. With a median follow-up of approximately 7 years, we aimed to minimize potential biases in the analysis through propensity score-matched pairs and competing risk analysis, ensuring a

robust evaluation of the long-term impact of NUC therapy. However, this study has inherent limitations as a retrospective observational cohort study, including reliance on ICD-code based operational definitions for the variables used in the analysis. Furthermore, using NHIS data, it can be assumed that NUC treatment was administered based on well-established clinical indications. However, although the number of such cases may be small, it remains unclear how differences in AD incidence might be affected by NUC use or non-use outside of insurance coverage or due to individual patient preferences. Additionally, we were unable to account for certain variables not included in the study, such as environmental factors (e.g., alcohol consumption and smoking), other causes of chronic hepatitis associated with AD (e.g., steatotic liver disease), and genetic risk factors, all of which may influence the outcomes. Furthermore, the impact of unmeasured variables, including baseline and serial laboratory data on viral status and chronic inflammation (e.g., viral DNA, eAg, eAb, AST, ALT), on the relationship between NUC use and AD incidence remains uncertain. In addition, from the perspective of chronic liver disease in CHB patients, NUC use carries the potential for both reducing neuroinflammation due to chronic liver inflammation and contributing to mitochondrial damage from long-term therapy. However, this study was unable to uncover any hidden mechanisms beyond the observed clinical phenotype. Therefore, it remains unclear whether a similar pattern exists in other types of ND that share theoretical mechanisms with AD. Additionally, this study did not aim to compare different types of antiviral agents, so we are unable to determine whether there are differences in AD incidence based on specific antiviral therapies. Similarly, differences related to CHB subtypes, and racial or ethnic variations could not be assessed. Further research is needed to determine whether similar results are observed in other subtypes of CHB or in different regions.

Conclusion

Our study suggests that NUCs reduce the risk of AD in patients with CHB. Given the inevitable prolonged use of NUCs for CHB suppression and the transition into an aging society, it is crucial to establish a management framework for long-term NUC therapy and a screening strategy for high-risk AD patients.

Abbreviations

AD	Alzheimer's disease
CHB	Chronic hepatitis B virus
CIs	Confidence intervals
HRs	Hazard ratios
ND	Neurodegenerative disease
NHIS	The Korea National Health Insurance Service
NUCs	Nucleos(t)ide analogs
PYs	Person-years

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-025-01729-3.

Supplementary Material 1

Author contributions

JL, HS, and HIK were involved in the study concept and design, data acquisition, data analysis, interpretation, drafting of the manuscript, and critical revision of the manuscript. HG and SJJ were involved in data acquisition, data analysis and interpretation. HIK was involved in study supervision. All authors were responsible for the data acquisition and critical revision of the manuscript and approved the final version.

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Data availability

Data used in this study are maintained by the Korea National Health Insurance Service (NHIS, https://nhiss.nhis.or.kr), and available upon submitting a proposal to be approved by the NHIS.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. 2023-04-039). The need for informed consent was waived due to the usage of de-identified data.

Competing interests

The authors declare no competing interests.

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