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ORIGINAL ARTICLE

Statin use and risk of progression to liver cirrhosis in chronic hepatitis B independent of conventional risk factors: A nationwide study

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Abstract

Many studies have elucidated the protective associations of statin use with liver cancer or mortality, but studies examining statin's effect on the risk of progression to liver cirrhosis considering medical/metabolic conditions or lifestyle factors are lacking. We aimed to assess statin's benefit independent of conventional risk factors. We identified 25,033 pairs of statin users (using statins for ≥90 days) and nonusers among patients with chronic hepatitis B (CHB) in the Republic of Korea's National Health Insurance Service database from 2010 to 2018. The primary endpoint was progression to cirrhosis from an inactive carrier or simple CHB. The cumulative probability was plotted using the Kaplan-Meier method. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were estimated using the multivariable Cox proportional hazard model. During a 218,472 person-year follow-up, 2210 incident cases of progression to cirrhosis occurred. The 5-year cumulative risks were 4.0% and 6.3% in statin users and nonusers, respectively ($p < 0.001$). Statin use was significantly associated with a decreased risk of progression to cirrhosis (aHR, 0.59; 95% CI, 0.55–0.65; $p < 0.001$), after adjusting for age, sex, hypertension, diabetes, dyslipidemia, antiviral therapy, aspirin use, metformin use, nonstatin medication for dyslipidemia, smoking, drinking, obesity, exercise, and liver dysfunction. This protective association was still significant in a dose–response manner and with different time lags for outcomes. *Conclusion*: Statin use is associated with a decreased risk of progression to cirrhosis among patients with CHB, independent of metabolic and lifestyle factors. Future studies are required to validate this observation.

Jin-Ha Yoon and Beom Kyung Kim contributed equally to this work.

INTRODUCTION

Chronic hepatitis B virus (HBV) infection has been a major public health concern affecting approximately 300 million people worldwide, especially in HBV-endemic areas, such as East Asian countries.[1–3] If left untreated, this chronic liver disease (CLD) can eventually lead to liver cirrhosis (LC), hepatocellular carcinoma (HCC), and hepatic decompensation.[4,5] Once the clinical phases progress from simple chronic hepatitis B to LC, the risk of developing hepatic decompensation and/or HCC as well as liver-related mortality increases substantially.

As a persistently high level of HBV replication is associated with an increased risk of LC, long-term antiviral therapy (AVT) using potent oral nucleos(t)ide analogs (e.g., entecavir or tenofovir disoproxil fumarate), which can effectively lead to virologic and biochemical remission, can remarkably reduce the risk of transition to LC.[6,7] However, because disease progression itself occurs by complex pathways involving interaction among viral, host, and environmental factors, AVT alone cannot eliminate the risk of disease progression.

Statins (3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors), which have been widely used to treat dyslipidemia and cardiovascular diseases, are one of the medications being evaluated regarding their preventive effects on disease progression of CLDs.[8] Because they have proapoptotic and antiproliferative properties with modulation of the cell cycle as well as anti-invasive and immunomodulatory properties along with a lipid-lowering effect, *in vitro* and preclinical studies have also suggested their potential therapeutic application as an ancillary disease modifier among patients with CLDs.[9–12] Even though there have been many studies regarding the chemopreventive effect of statins against HCC development among patients with chronic HBV infection, there is a lack of studies that have evaluated the independent association of statins with the development of LC and/or hepatic decompensation with consideration of other metabolic conditions and lifestyle factors. Therefore, we aimed to assess the protective association of statins with the risk of LC development, considering other conventional risk factors, including metabolic conditions and lifestyle habits, in a large-scale nationwide cohort of patients with chronic HBV infection in the Republic of Korea.

MATERIALS AND METHODS

Data source and study population

Data in the Republic of Korea's National Health Insurance Service (NHIS) database from January 1, 2010, to December 31, 2018, were used in this nationwide cohort study. Patients' demographic information, outpatient visit, or hospitalization dates; major diagnostic codes; medical examination findings and treatment; detailed medication prescription statements; and health examination data are stored in this database. The International Classification of Diseases, Tenth Edition (ICD-10) codes used in this investigation are summarized in Table S1.

Patients with chronic hepatitis B who were older than 20 years of age and underwent a health examination that was listed in the database were initially assessed for this study. Patients who had visited as outpatients or were hospitalized between 2010 and 2012 were included. The exclusion criteria were as follows: (1) patients prescribed a statin in 2010, (2) patients in the medical aid program, (3) patients previously diagnosed with LC before the index date (described later), (4) patients with newly diagnosed LC within the 6-month follow-up, (5) patients with hepatitis C virus (HCV) or human immunodeficiency virus coinfection, (6) patients with a history of malignancy, (7) patients with a history of alcoholic liver disease, and (8) patients with a history of myocardial infarction or ischemic stroke.

Statin user was defined as a patient who had been taking any kind of statin (i.e., simvastatin, pravastatin, rosuvastatin, atorvastatin, pitavastatin, fluvastatin, and lovastatin) for ≥90 days during the follow-up period. To set the index date of nonusers to control for immortal time bias, prescription time distribution matching (PTDM) was used. PTDM matches the index date of nonusers with the index date of statin users randomly with replacement.[13] All diseases were defined using ICD-10 codes with the criteria of three or more outpatient visits or one or more hospitalizations. In case of decompensated LC, the diagnosis was decided based on the ICD-10 code and claim code for the procedure related to the diagnosis (Table S1).

This study was approved by the institutional review board, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The need for informed consent was waived because of the retrospective nature of this study.

Main outcomes

The primary endpoint was new-onset LC, defined as liver cirrhosis or liver fibrosis development with and without decompensation. Death and orthotopic transplantation (OLT) were considered as competing risk events. The secondary endpoints were all-cause/liver-related mortalities. The first day of an outpatient visit or hospitalization for diagnosis was used to determine the date of newly developed LC. The date of LC occurrence, death, or the end of the study period, which was December 31, 2018, was set as the last follow-up date.

Definition of cohort variables

History of diseases, including hypertension, diabetes, and dyslipidemia, was defined according to the ICD-10 codes. The criteria used for statin users were also used to define medication history, including AVT against chronic hepatitis B; metformin use; nonstatin dyslipidemic medication use, including bezafibrate, fenofibrate, gemfibrozil, ciprofibrate, nicotinic acid, omega 3, and ezetimibe; and aspirin use, which was defined as a prescription ≥90 days during the follow-up period. Tenofovir, entecavir, adefovir, clevudine, lamivudine, and peg-interferon alpha were included in AVT against chronic hepatitis B. According to the health examination data, lifestyle factors were defined as follows: patients were classified as nonsmokers, ex-smokers, or current smokers based on their smoking history; patients with alcohol consumption >50 g of alcohol per week in women or 70 g of alcohol per week in men were defined as alcohol drinkers; and patients who did high-intensity exercise, median-intensity exercise, or walking 3 times or more per week were classified as the exercise group while others were classified as the nonexercise group. Body mass index (BMI) was used to categorize obesity as underweight (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), or obese (≥25 kg/m^2), according to the Asian guidelines.[14] Liver dysfunction, which could reflect various liver diseases, including nonalcoholic fatty liver disease, was defined if there was presence of any of the following: aspartate transaminase level ≥51 IU/L; alanine transaminase level ≥46 IU/L; and gamma-glutamyltransferase ≥78 IU/L in men or ≥46 IU/L in women.[15] The low-density lipoprotein (LDL) cholesterol group was classified into five groups: <70, 70 to <100, 100 to <130, 130 to <160, and ≥160 mg/dL. Metabolic factors were defined based on the updated Adult Treatment Panel III (ATPIII) criteria for Asians.[16] Fatty liver index (FLI) was calculated by a complex formula of BMI, waist circumference, triglyceride (TG), and gamma-glutamyltransferase.[17]

Statistical analysis

From the selected patients, statin users were matched with nonusers, using propensity scores at a ratio of 1:1. Propensity scores were estimated for statin use by using variables including age, sex, hypertension, diabetes, dyslipidemia, AVT, aspirin use, metformin use, nonstatin dyslipidemic medication use, smoking history, alcohol history, obesity, exercise, and liver dysfunction. The propensity score was calculated based on a logistic regression model, and the absolute standardized mean difference was used to examine the balance of covariate distribution between statin users and nonusers.[18] The average incidence rates of LC were calculated as the number of events per 1000 person-year (PY) of follow-up. The cumulative incidences of LC development and all-cause mortality for statin users and nonusers were plotted using the Kaplan-Meier method. The log-rank test was used to compare the differences in HCC and all-cause mortality between the two groups. The adjusted hazard ratio (HR) with 95% confidence interval (CI) of the cause-specific relative hazard was calculated using a multivariable Cox proportional hazard model. Age, sex, hypertension, diabetes, dyslipidemia, AVT, aspirin use, metformin use, nonstatin medication use for dyslipidemia, smoking history, alcohol history, obesity, exercise, and liver dysfunction were used as covariates to estimate the adjusted HRs of LC progression, all-cause mortality, and liver-related mortality. The variance inflation factor value was used to measure multicollinearity of the models.

For dose-dependent analyses, patients were stratified into four groups based on the duration of statin use to examine the dose–response relationship: <90 days, 90–364 days, 365–1094 days, and ≥1095 days. Subgroup analyses were performed by stratifying each variable that was used as a covariate. Moreover, the association between statin use and progression to LC was examined in the subgroups stratified by alcohol consumption and AVT.

As a sensitivity analysis, the cause-specific Cox proportional hazard model and Fine and Gray regression were performed to estimate adjusted or subdistribution HRs with consideration of competing risks, which were death and OLT in this study. Moreover, different time lags of 1, 2, 3, and 4 years for LC or competing risk events were applied.[19] Patients with LC or competing risk events within the time lag were excluded from the multivariable Cox analysis. Additionally, TG, LDL, and high-density lipoprotein (HDL) cholesterol were additionally adjusted and stratified in the models. Finally, adjusted HRs were calculated based on metabolic syndrome components, and stratification analyses were based on the number of metabolic syndrome components.

The independent *t* test and chi-squared test were used to assess differences between statin users and nonusers for continuous and categorical data, respectively. SAS, version 9.2 (SAS Institute, Cary, NC, USA) and R software (version 4.0.3, http://cran.r-project.org/) were used to perform all statistical analyses. A CI of 95% was calculated for all estimates, and statistical significance was defined as a two-tailed $p < 0.05$.

RESULTS

Baseline characteristics

After applying the exclusion criteria and 1:1 propensity score matching of the entire population, a total of 50,066 patients (25,033 pairs of statin users and

nonusers) over the 218,472 PY follow-up were finally included in this study (Figure S1). Among the statin users of the entire cohort, most patients (87.0%) took statins based on their history of hypertension, diabetes, or dyslipidemia, and statin users were more likely to have hepatic steatosis defined by FLI ≥ 30 compared to nonstatin users (47.4% vs. 28.8%; $p < 0.001$).

Baseline characteristics of patients before and after matching stratified by statin use are summarized in Table 1. The absolute standardized mean difference of each variable was <0.1, implying adequate balance of covariate distribution (Figure S2). The mean age ± SD of the matched cohort was 50.2 ± 10.6 years. The proportion of men in the matched cohort was 57.9%. Statin user was associated with a significantly higher prevalence of male sex, metformin use, aspirin use, nonstatin medication use for dyslipidemia, liver dysfunction, current smoker, alcohol drinker, and higher FLI than nonstatin user in the matched cohort.

Clinical outcomes during the follow-up and the association between statin use and progression to LC

During the follow-up, 2210 (4.4%) patients newly developed LC. Of the newly diagnosed patients, 2066 (93.5%) were initially diagnosed with compensated LC while the other 144 (6.5%) were initially diagnosed with complications of LC, including ascites, esophageal bleeding, hepatic failure, hepatorenal syndrome, peritonitis, and hepatic encephalopathy. The average incidence rates of progression to LC were 7.5 per 1000 PY (95% CI, 7.0–8.1) and 12.7 per 1000 PY (95% CI, 12.0–13.4) in the statin-user and nonuser groups, respectively. The 5-year cumulative incidence rates of progression to LC were 4.0% and 6.3% in the statin user and nonuser groups, respectively ($p < 0.001$). The number of cases of new-onset all-cause mortality, liver-related mortality, and OLT in the cohort were 843 (1.7%), 269 (0.5%), and 48 (0.1%), respectively. The cumulative incidence plots of progression to LC and all-cause mortality by statin use are shown in Figure 1. The cumulative incidences of both progression to LC and mortality were significantly lower in statin users than in nonusers ($p < 0.001$). Overall, a total of 95 patients stopped statins within 90 days from hepatic decompensation.

The crude HR of LC for statin use was 0.59 (95% CI, 0.54–0.65) in the univariate analysis. The adjusted HRs of LC for statin use were 0.59 (95% CI, 0.55–0.65) in the multivariable Cox proportional hazard model (Table 2). The adjusted HRs of all-cause mortality and liver-related mortality by statin use was 0.80 (95% CI, 0.70–0.92) and 0.53 (95% CI, 0.41–0.69; $p < 0.001$), respectively. A duration-dependent association of statin use with a reduction in the risk of progression to LC was significant (p for trend < 0.001). Adjusted HRs of LC by 90–364, 365–1094, and ≥1095 days of statin use in the multivariable Cox models were 0.70 (95% CI, 0.61–0.80), 0.59 (95% CI, 0.51–0.67), and 0.53 (95% CI, 0.47–0.60), respectively (Table 3).

Subgroup analysis according to various medical/metabolic conditions or lifestyle factors

Subgroup analyses of the multivariable Cox model showed that the association between statin use and a reduced risk of progression to LC was significant regardless of age, sex, hypertension, diabetes, dyslipidemia, AVT, metformin use, aspirin use, liver dysfunction, smoking history, alcohol history, and obesity (Figure 2). The relationship was more pronounced in the groups of women, nondiabetes, dyslipidemia, and nonmedication for AVT, metformin use, and aspirin use than in the other groups. With subgroups stratified by AVT and alcohol consumption, statin use was significantly associated with a reduced risk of progression to LC in all subgroups (Table S2).

Sensitivity analysis

In the sensitivity analysis, adjusted or subdistribution HRs of progression to LC for statin use in the cause-specific Cox model and Fine and Gray regression were 0.60 (95% CI, 0.55–0.65) and 0.60 (95% CI, 0.55–0.65) (Table S3). Moreover, adjusted HRs of progression to LC for statin use in the multivariable Cox model were 0.62 (95% CI, 0.57–0.69), 0.66 (95% CI, 0.59–0.75), 0.70 (95% CI, 0.61–0.81), and 0.69 (95% CI, 0.57–0.83) for the 1-, 2-, 3-, and 4-year additional time lags, respectively (Table S4). After additional adjustment of cholesterol levels, including LDL, TG, and HDL, statin use was still significantly related to a decreased risk of progression to LC with an HR of 0.64 (95% CI, 0.59–0.71). Stratification analysis based on cholesterol types and levels also showed a significant relationship between statin use and the incidence of LC (Table S5). Considering the metabolic component of each patient based on the ATPIII criteria, the protective association of statin use with the progression to LC was not attenuated in either adjustment or stratification (HR, 0.59; 95% CI, 0.54–0.65; Table S6).

DISCUSSION

Our study on the nationwide cohort of patients with chronic HBV infection showed that statin use has a significant protective association with progression to LC, independent of other known risk factors of LC. Such significant associations were also demonstrated in a duration-dependent manner and with different additional

TABLE 1 Baseline characteristics of patients by statin use

	Before matching (n = 192,780)			After matching (n = 50,066)		
	Statin user (n = 32,307)	Nonuser (n = 160,473)	*p* value	Statin user (n = 25,033)	Nonuser (n = 25,033)	*p* value
Age (years), mean (SD)			<0.001			0.026
	51.7 (10.2)	44.4 (11.0)		50.1 (10.0)	50.3 (11.2)	
Sex			<0.001			<0.001
Male	17,576 (54.4%)	95,708 (59.6%)		14,494 (57.9%)	14,074 (56.2%)	
Female	14,731 (45.6%)	64,765 (40.4%)		10,539 (42.1%)	10,959 (43.8%)	
Hypertension			<0.001			0.083
No	15,826 (49.0%)	131,033 (81.7%)		14,377 (57.4%)	14,185 (56.7%)	
Yes	16,481 (51.0%)	29,440 (18.3%)		10,656 (42.6%)	10,848 (43.3%)	
Diabetes			<0.001			<0.001
No	21,931 (67.9%)	147,405 (91.9%)		18,129 (72.4%)	19,129 (76.4%)	
Yes	10,376 (32.1%)	13,068 (8.1%)		6904 (27.6%)	5904 (23.6%)	
Dyslipidemia			<0.001			0.063
No	10,120 (31.3%)	132,377 (82.5%)		9904 (39.6%)	10,108 (40.4%)	
Yes	22,187 (68.7%)	28,096 (17.5%)		15,129 (60.4%)	14,925 (59.6%)	
Antiviral therapy			<0.001			0.039
No	21,381 (66.2%)	93,425 (58.2%)		15,346 (61.3%)	15,570 (62.2%)	
Yes	10,926 (33.8%)	67,048 (41.8%)		9687 (38.7%)	9463 (37.8%)	
Metformin use			<0.001			<0.001
No	24,191 (74.9%)	153,439 (95.6%)		19,951 (79.7%)	20,893 (83.5%)	
Yes	8116 (25.1%)	7034 (4.38%)		5082 (20.3%)	4140 (16.5%)	
Aspirin use			<0.001			<0.001
No	24,889 (77.0%)	153,929 (95.9%)		20,729 (82.8%)	21,193 (84.7%)	
Yes	7418 (23.0%)	6544 (4.1%)		4304 (17.2%)	3840 (15.3%)	
Nonstatin dyslipidemic medication use			<0.001			<0.001
No	28,542 (88.4%)	157,418 (98.1%)		22,422 (89.6%)	22,949 (91.7%)	
Yes	3765 (11.6%)	3055 (1.9%)		2611 (10.4%)	2084 (8.3%)	
Liver dysfunction			<0.001			<0.001
No	23,184 (71.8%)	120,454 (75.1%)		17,552 (70.1%)	18,185 (72.6%)	
Yes	9123 (28.2%)	40,019 (24.9%)		7481 (29.9%)	6848 (27.4%)	
Smoking history			<0.001			0.012
Nonsmoker	19,186 (59.4%)	93,873 (58.5%)		14,427 (57.6%)	14,676 (58.6%)	
Ex-smoker	5706 (17.7%)	27,322 (17.0%)		4637 (18.5%)	4667 (18.6%)	
Current smoker	7415 (22.9%)	39,278 (24.5%)		5969 (23.9%)	5690 (22.8%)	
Alcohol drink			<0.001			0.002
No	24,191 (74.9%)	119,672 (74.6%)		18,508 (73.9%)	18,808 (75.1%)	
Yes	8116 (25.1%)	40,801 (25.4%)		6525 (26.1%)	6225 (24.9%)	
Obesity			<0.001			0.007
Underweight	430 (1.3%)	6251 (3.9%)		415 (1.7%)	456 (1.8%)	
Normal	8796 (27.2%)	67,417 (42.0%)		7589 (30.3%)	7428 (29.7%)	
Overweight	8285 (25.7%)	38,942 (24.3%)		6723 (26.9%)	6515 (26.0%)	
Obese	62,659 (45.8%)	47,863 (29.8%)		10,306 (41.1%)	10,634 (42.5%)	
Fatty liver index			<0.001			<0.001
<30	15,936 (52.6%)	106,108 (71.2%)		12,812 (54.6%)	13,991 (59.9%)	
≥30	14,359 (47.4%)	42,963 (28.8%)		10,636 (45.4%)	9380 (40.1%)	

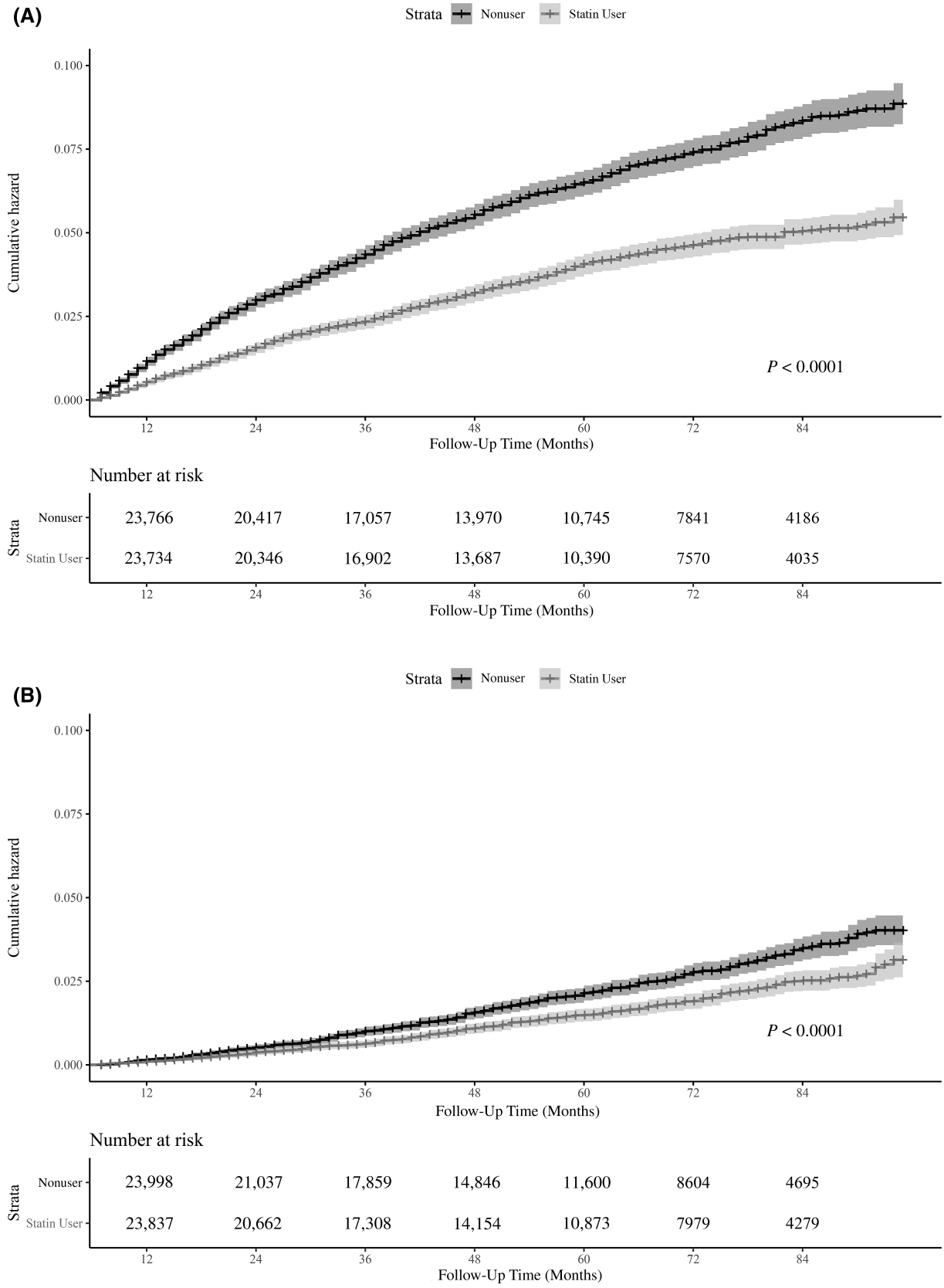

FIGURE 1 Cumulative incidence plots of the outcomes by statin use. (A) Liver cirrhosis. (B) Mortality.

TABLE 2 Adjusted HRs and 95% CIs of progression to liver cirrhosis and all-cause/liver-related mortality by statin use

	Progression to liver cirrhosis		All-cause mortality		Liver-related mortality	
	adjusted HR (95% CI)	*p* value	adjusted HR (95% CI)	*p* value	adjusted HR (95% CI)	*p* value
Statin use						
No	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.60 (0.55–0.65)	<0.001	0.80 (0.70–0.92)	0.002	0.53 (0.41–0.69)	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 3 Duration-dependent relationship between statin use and progression to liver cirrhosis

Statin use (days)	At risk, n	HCC, n (%)	Adjusted HR (95% CI)	*p* value
<90	25,033	501 (2)	1.00 (reference)	
90–364	8006	130 (1.6)	0.70 (0.61–0.80)	<0.001
365–1094	9151	124 (1.4)	0.59 (0.51–0.67)	<0.001
≥1095	7876	88 (1.1)	0.53 (0.47–0.60)	<0.001

Abbreviations: CI; confidence interval; HCC, hepatocellular carcinoma; HR; hazard ratio.

time lags for the outcome and the competing risk event. Moreover, all subgroup analyses with other medications and lifestyle factors showed a significant relationship between statin use and a reduced risk of progression to LC. The risk of all-cause and liver-related mortality was also significantly lower in the statin-user group.

To date, several studies have assessed the risk of LC and related complications with statin use.[8] In a systematic review, statin use was related to a reduced risk of hepatic decompensation and mortality in patients with various CLDs, such as HBV, HCV, and alcoholic liver disease, including compensated cirrhosis and noncirrhotic CLD. Furthermore, numerous studies have elucidated that patients with LC who received statins had a significantly lower incidence of HCC and mortality,[15,20] suggesting that LC and other CLDs should be established as a new indication for statin use.[21,22] Nonetheless, to the best of our knowledge, there is a paucity of studies to show that statin use is associated with a reduced risk of progression to LC, especially in patients with chronic HBV infection. The study by Huang et al.[23] showed an association between statin use and a reduced risk of LC in patients with chronic HBV infection; however, that study did not consider any additional time lag for the outcome; any lifestyle factor, including smoking and alcohol consumption[24]; or any compelling indication for statin use, including myocardial infarction and ischemic stroke.

The protective association between statin use and LC can be explained by several plausible mechanisms. Critical pathways related to hepatic ischemic and reperfusion injury include the inducible nitric oxide synthase–nitric oxide and Kruppel-like factor 2 (KLF2) pathways.[25,26] Numerous studies have reported that statins, especially simvastatin, have a role in preventing the burst of proinflammatory nitric oxide and ischemic injuries by inducing the expression of KLF2.[27,28] Despite the explanatory mechanisms of the protective association of statin use with LC, regardless of the underlying CLD, most randomized clinical trials have focused on the outcome of the hepatic decompensation event or mortality in patients with LC.[9,29] Furthermore, to our knowledge, ongoing randomized trials are also mostly focused on patients with LC. Considering the plausible mechanisms, it is necessary to implement randomized clinical trials in patients with CLDs, including HBV, HCV, and alcoholic liver disease, such as LC.

Even though the significant protective effect of statin use on progression to LC compared to nonusers was maintained across subgroups according to co-medication, we confirmed that adjusted HRs between statin users and nonusers may vary considerably according to co-medications. Considering that AVT,[30,31] metformin,[32] and aspirin[33] have an anti-inflammatory effect, which is primarily a mechanism similar to that of statins, the additional protective effect of statin use may decrease with use of co-medications. Further studies are required to clarify such interactions among medications. Statin use was also associated with a decreased risk of LC in patients with liver dysfunction or alcohol consumption. Despite hesitancy in prescribing statins to patients with liver dysfunction because of a hepatic adverse effect,[34] statins could be used cautiously under the periodic surveillance of physicians, according to our study results.

Our study has several strengths. First, using the representative nationwide database, which includes 97.2% of the entire South Korean population, all patients with chronic HBV infection in the Republic of Korea were included in the study.[35] More than 50,000 patients were enrolled even after applying the exclusion criteria and propensity score matching, and our study included a larger number of patients than a previous study.[23] Our incomparable large sample size of recruited patients allowed us to investigate and generalize the relationship between statin use and a

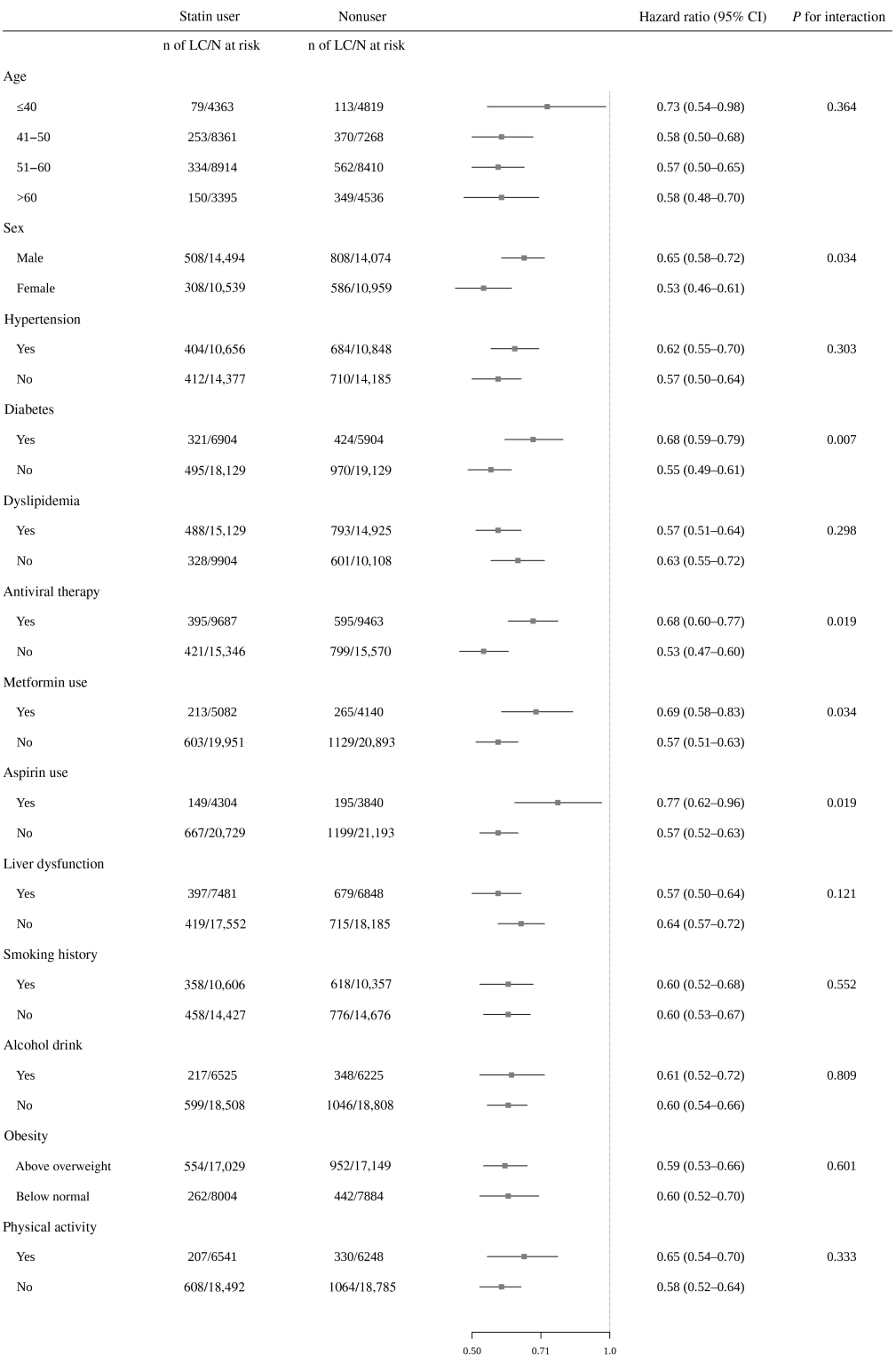

FIGURE 2 Subgroup analysis of progression to liver cirrhosis by statin use. CI, confidence interval.

decreased risk of progression to LC in patients with chronic HBV infection. Second, the well-controlled exclusion criteria and various analytic methods were applied in our study. During the patient selection process, we set a 1-year window for statin use, outcome, and competing risk event. Patients who received medical aid from the government were excluded to eliminate outliers with regards to socioeconomic status. Moreover, PTDM was performed to minimize immortal time bias, and patients with a compelling indication for statin use, including myocardial infarction and ischemic stroke, were excluded. Additionally,

propensity score matching was performed, resulting in well-balanced variables. In statistical analyses, the cause-specific Cox proportional hazards model and Fine and Gray regression were performed, considering the competing risk events, and dose-dependent analysis was conducted by dividing statin users into four groups according to the duration of statin use. Several sensitivity analyses were further performed, and all the results supported the protective association between statin use and progression to LC.

There are also several limitations to this study. First, the causal relationship between statin use and the risk reduction of LC could not be clarified in this observational study. In a similar context, in order to compare the ability to decrease the risk of liver disease progression among medications (statin vs. other medications, such as AVT, metformin, and aspirin) quantitatively, further prospective experimental studies considering the interaction between statin and other anti-inflammatory medications/comorbidities are required. Second, because of the inherent weakness of a nationwide cohort study, there could be a limitation with respect to the accuracy of diagnosis and patient compliance. Although poor compliance with treatment might have occurred, this overestimation of dose might underestimate the protective association of statin use. Furthermore, to achieve high accuracy of diagnosis, our study applied the criteria of three or more outpatient visits or one or more hospitalizations. Third, primarily owing to the limited availability of detailed information in the NHIS database, we cannot assess the different effect of lipophilic versus hydrophilic statins on progression to LC. Although several studies have suggested that lipophilic statins should have a more favorable effect on preventing HCC development than hydrophilic statins,[36,37] there has been no study comparing its different effect regarding the progression to LC among the HBV-infected population. It can be conjectured that lipophilic statins have stronger chemoprotective effects than hydrophilic statins owing to better fat solubility and membrane permeability as well as increasing nitric oxide availability.[10,38] Hence, further studies are required to validate this hypothesis. Similarly, we could not perform analysis using parameters indicative of fibrotic burden (i.e., change of type-4 collagen level or fibrosis-4 index).[39] However, to resolve such a limitation in part, we assessed progression of liver cirrhosis by using not only the diagnostic code but also the development of various complications. Lastly, given that most patients were infected with HBV genotype C2 through vertical transmission in the Republic of Korea,[40,41] the current study's results might not be generalizable to other ethnicities.

In conclusion, statin use in patients with chronic HBV infection has a significant protective association with progression to LC independent of conventional risk factors. This association was still significant in a duration-dependent manner and with different time lags. Further studies should be implemented to clarify the causal relationship.

AUTHOR CONTRIBUTIONS

Study concept and design and critical revision of the manuscript for important intellectual content: Byungyoon Yun, Jin-Ha Yoon, and Beom Kyung Kim. Acquisition of data: Beom Kyung Kim. Analysis, interpretation of data, and statistical analysis: Byungyoon Yun and Jin-Ha Yoon. Drafting the manuscript: Byungyoon Yun, Sang Hoon Ahn, and Beom Kyung Kim. Obtaining funding: Jin-Ha Yoon. Administrative, technical, or material support: Sang Hoon Ahn and Beom Kyung Kim. Study supervision: Jin-Ha Yoon and Beom Kyung Kim.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest pertaining to this research.

DATA AVAILABILITY STATEMENT

Due to the policy of the NHIS data used in this study, raw data remain confidential and cannot be shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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