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Causal Analyses of Statin to Prevent Liver Disease Progression: A Nationwide Study Using Superlearning Targeted Maximum Likelihood Estimation

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Abstract Many studies have shown that statins reduce the risk of progression to liver cirrhosis (LC) and hepatocellular carcinoma (HCC) among at-risk populations. However, causality has not been proved. This study examined whether statins could prevent LC and HCC in patients with progressive and worsening chronic liver disease, using a robust methodology for causality. Between 2002 and 2013, 52,145 patients with chronic liver diseases were identified from the National Health Insurance Service database in South Korea. The inverse probability weighting (IPW) and superlearning targeted maximum likelihood estimation (TMLE) were used to assess the causality of statin use on the risk of LC and HCC, adjusting for sex, age, comorbidities, and co-medications. Multivariable superlearning TMLE revealed that statin use was associated with reduction in the incidence risk of LC (Marginal odds ratio (MOR) 0.59, 95% confidence interval [CI] 0.50-0.65) and HCC (MOR 0.59, 95% CI 0.50-0.67). Such a protective effect was more evident with atorvastatin and lipophilic statin. This population-based observational study indicated the benefit of statin use, particularly atorvastatin and lipophilic statin, for causally reducing the risk of LC and HCC.

Keywords IPW, TMLE, Liver cirrhosis, Hepatocellular carcinoma, Causality, 3-Hydroxy-3-methylglutaryl CoA reductase inhibitor

Introduction

To date it was unclear whether statins can be administered to patients with chronic liver disease such as non-alcoholic fatty liver disease (NAFLD) or viral hepatitis for the purpose of preventing liver cirrhosis (LC) and hepatocellular carcinoma (HCC).[1] No suitable treatment to directly reverse LC and normalize portal pressure via anti-fibrogenesis has been developed, and liver transplantation is only a limited option due to a shortage of resources. Likewise, although treatment modalities for HCC have shown remarkable development for two decades, the 5-year survival rate of patients with HCC is still disappointing. Therefore, pre-emptive intervention for preventing disease progression among at-risk populations is imperative to improve mortality, morbidity, and quality of life.[2,3]

Retrospective studies show that statins or 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, widely used to treat dyslipidemia and cardiovascular diseases, can reduce the risk of LC and HCC.[4,5] However, previous studies have explored only the association between statin use and the risk of LC and/or HCC, and no study has investigated the causality between statin use and clinical prognosis.[6-8] Also, there were no prospective randomized trials to adequately evaluate the causality of statins for LC and HCC.[9] Previous studies have been conducted based on the systematic review of the relation between statin use and LC or NAFLD.[10,11] However, there has been no observational studies long-term robust methods for causal inference.Re The current study used the targeted maximum likelihood estimation (TMLE), which combined the propensity score and g-formula and integrated it as a powerful estimation method in causality analysis.[12-15] The

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TMLE estimates double robust results[16,17] by controlling unexposed confounding factors. Studies have used ensemble and machine-learning algorithms to reduce potential bias in TMLE and make statistical inferences based on the efficient influence curve (IC).[18]

This study examined whether statins could prevent LC and HCC in patients with progressive and worsening chronic liver disease with superlearning targeted maximum likelihood estimation.

Methods

Study design and population

A population-based retrospective cohort study was conducted using the National Health Insurance Service-National Sample Cohort. The cohort of 1,040,488 participants was randomly selected from a target population of 46,605,433 individuals in 2002 from the National Health Information Database. The cohort, represented 2.2% of the eligible Korean population in 2002 and was followed for 11 years until 2013. The NHIS-NSC database contains demographic and socioeconomic information such as sex, residential area, health insurance type, income level, type of disability, birth and death records, medical bills, details of medical and prescription claims, and types of medical institutions.[19] Detailed prescription data included generic names of drugs, the date of prescription, and the amount and duration of medication for each drug.

We selected a total of 52,145 from 1,040,488 persons in 2002 as the initial samples using the following exclusion criteria: no information on sex, age, and income; age below 20 years with the reference date being 1 January 2002.; no liver disease before 1 January 2002; subjects who used statin from 1 January 2002 to 31 December 2002 (shown in Fig. 1). The persons with a pre-existing liver disease diagnosis were excluded at the entry point of January 1, 2002. A one-year washout period was implemented to further exclude individuals with any recorded liver disease. Given the nature of liver diseases, it was assumed that subjects without a liver disease record as of January 1, 2002, were unlikely to exhibit a liver disease diagnosis after January 1, 2003, if they were continuously followed up.

Assessment of statin exposure

The index date for statin use was defined as 1 January 2003, 1 year after the initiation of the cohort. The washout period of one year was implemented to minimize potential confounding effects from prior statin use. To reset the baseline risk of liver disease for all participants, all statin users were excluded from the study population during the washout period. By doing so, the effects of

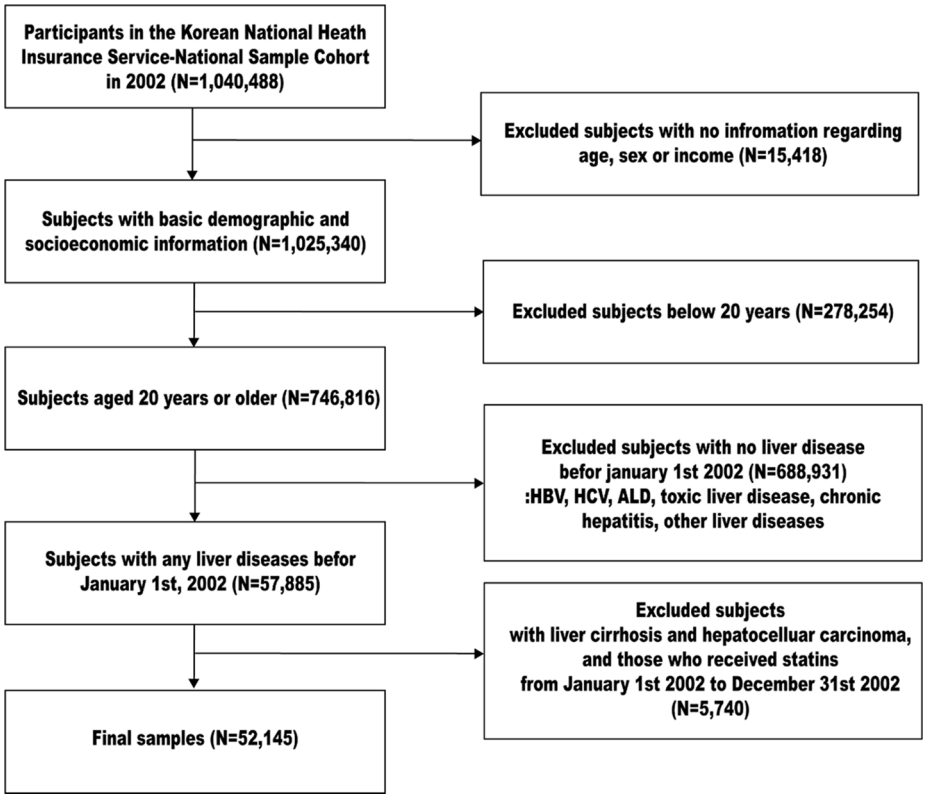

Fig. 1. Sample selection flow

statin use on liver cirrhosis and liver cancer incidence could be more accurately isolated. Statin use was identified as the prescription of statins on two or more occasions during admission or outpatient visits throughout the study period. Statin subtypes included simvastatin, lovastatin, fluvastatin, pravastatin, atorvastatin, and rosuvastatin. Statins were classified as hydrophilic (rosuvastatin, pravastatin) and lipophilic (atorvastatin, simvastatin, fluvastatin, pitavastatin, lovastatin). The magnitude of statin use was measured with a defined daily dose (DDD), a validated unit for measuring the average maintenance dose of a prescribed drug per day for an adult.[20] The earliest recorded initiation of statin treatment among the study subjects was on January 1, 2003, with some subjects commencing statin treatment at later dates. The follow-up period from the start of statin exposure to the incidence of the outcome varied among subjects. To account for these differences in the duration from the initiation of statin to the outcome, we differentiated between the total cumulative Defined Daily Dose (cDDD) over the entire exposure period and the annual cDDD in our analysis. A cDDD) was measured throughout the observation period and categories as following: 0-30, 30-180, 180-720, and 720 or more. The cDDD of statins per year was further classified as follows: (1) <30 cDDD per year, that is, used statin for less than two consecutive months per year, considering that clinicians often prescribe less than 0.5 DDD of statins in South Korea; (2) 30-120 cDDD per year; (3) >120 cDDD per year. We established specific criteria to differentiate between statin users and non-users based on cDDD. We categorized individuals as non-users of statins if their cDDD was less than 30 (cDDD<30). Conversely, we classified individuals as statin users if their cDDD was 30 or more (30≤cDDD). This approach allowed us to create a clear distinction between those who had minimal or no exposure to statins and those who had a significant level of exposure.

Outcome

The follow-up period for the study subjects was concluded upon the initial diagnosis of LC and HCC, or otherwise extended until 31 December 2013. The primary outcome of interest was the incidence of LC and HCC following statin exposure. To identify incidences of these diseases, we utilized the International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes K74 for LC and C22.0 for HCC, as detailed in Table S1. The ICD-10 codes of LC and HCC were considered valid only when the codes of clinical biochemistry tests and imaging diagnosis were accompanied those diagnoses. In South Korea, the presence of liver cirrhosis was in general determined by either histological evidence or clinical findings based upon the practice guideline from the Korean Association for the study of the Liver.[21,22] HCC was in general diagnosed by either histological evidence or with radiological findings determined by dynamic computed tomography and/or magnetic resonance imaging (nodule >1 cm with arterial hypervascularity and portal/delayed-phase washout).[23,24] However, in subjects where LC and HCC were concurrently documented, no distinction was made between these conditions. While there was an interest in analyzing subjects in whom HCC developed after LC, the limited duration of the study and the rarity of such occurrences prevented this analysis. Moreover, in situations where LC was recorded following the onset of HCC, it was challenging to ascertain whether LC actually developed after HCC. Consequently, subjects with overlapping diagnoses of LC and HCC were not analyzed separately.

Confounders

Confounder selection was based on a causal directed acyclic graph (shown in Fig. S1). Confounders included age and sex at the index date. Age was categorized as 20-39, 40-59, and 60 over. Baseline comorbidities at the index date included cardiovascular diseases, cerebrovascular diseases, hypertension, and diabetes with known associations with LC[25-30] and HCC[31-33] (Table S1). The numbers of patient records from 2002 to 2003 were controlled as indicators of prior clinical evaluation. Concomitant LC-related[34,35] and HCC-associated medications,[34,36-38] including anti-diabetic drugs, anti-hypertensive drugs, and lipid-lowering agents (except statins), were also controlled (Table S2). Baseline statistics for confounding variables, including age, comorbidities, and concomitant medications, were determined as of January 1, 2003. And in order to control for confounders in the diagnostic process, we employed a method of cross-verifying test item codes used in national data with ICD-10 codes (Table S3).

Statistical analysis

In the study, baseline characteristics of participants who developed LC or HCC were compared with those who did not develop these conditions. Continuous variables were analyzed using the t-test, while categorical variables were evaluated using the Chi-square test. We used inverse probability weighting (IPW) and targeted maximum likelihood estimation (TMLE) as our methods for estimating causality. Targeted maximum likelihood estimation (TMLE) was used to estimate the causal effect.[15,39-41] The Super-Learner is a type of ensemble learner that estimates the average treatment effect by adaptively combining different machine learning algorithms to avoid bias caused by incorrect models. In particular, we chose a weighted combination of predictions that minimizes the mean squared error obtained by cross-validation.[15]

Superlearner algorithm used in the TMLE ensemble is an ensemble learner that adaptively combines different machine learning algorithms to estimate parameters such as Q0 AW (the outcome model) and gAW (the propensity score). The Superlearner algorithm is integral to the steps involved in calculating the average treatment effect (ATE) and the marginal odds ratio (MOR) in the context of this study (Appendix 1). Step 1 involves predicting the outcome model using standard logistic regression to estimate the conditional mean of the outcome, given treatment and baseline covariates. Step 2 entails predicting the propensity score using logistic regression to estimate the probability of receiving treatment, given the covariates. Step 3 involves using clever covariates and estimating ε, similar to inverse probability weights, to adjust the model. Step 4 updates the prediction of Q0 AW and Q1 AW, adjusting the outcome model's predictions with the previously estimated ε. Step 5 estimates the ATE and MOR by calculating the average treatment effect and marginal odds ratio based on the updated predictions. Step 6 involves statistical inference and calculating the 95% CI by constructing estimators for statistical inference and calculating standard errors for the estimated effects. The integration of the Superlearner into the TMLE framework aims to circumvent biases due to incorrect model specifications. Superlearner augments the initial logistic models by incorporating a varied assortment of algorithms, such as parametric and nonlinear regressions, shrinkage estimators, and regression trees, chosen for their predictive capabilities. Rather than selecting a singular algorithm based on the lowest anticipated prediction error through cross-validation, Superlearner employs a weighted ensemble of these algorithms, optimizing the model by minimizing the cross-validated mean squared error, thus enhancing predictive accuracy and reducing bias.[15] We conducted causal inference analysis to investigate the impact of statin use on the incidence of LC and HCC, with estimating the marginal odds ratio (MOR) as a measure. We also conducted subgroup analyses based on statin dose (cDDD), statin types, and underlying liver disease types. To assess the robustness of the treatment effect estimate for the unmeasured confounding, a sensitivity analysis using the multiple causal inference method, was performed. We compared the average treatment effect (ATE) obtained from our primary analysis with results from other causal inference methods, including propensity score matching, IPW, and superlearning TMLE. Data were analyzed according to statin type. Statistical analyses were performed with STATA version 17.0 (Stata Corporation LLC, College Station, USA) and the package TMLE and SuperLearner[42] of R version (4.0.2).

Results

Table 1 presents the characteristics of the final sample spanning from 2003 to 2013. Among the 52,145 subjects, 5.7% (N=2,964) were developed LC, of which 68.5% were males; 53.3% were 40-59 years old. Those who developed HCC were 3.6% (N=1,851) among the 52,145 subjects. The prevalence of diabetes was observed to be significantly higher in subjects who developed LC and HCC compared to those who did not develop these conditions. ($p<0.001$). The prevalence of underlying liver diseases was higher in subjects who developed LC and HCC compared to those who did not develop these conditions for all types of liver diseases ($p<0.001$ for all types). Patients with LC and HCC were more likely to receive oral anti-diabetics and anti-hypertensive drugs (Table 1).

To assess the positivity assumption for estimators that rely on the propensity score, including the TMLE, we examined the estimated propensity score distribution. Figure 2 displays the histogram of the estimated propensity scores for the statin use group and non-use group. The distribution of propensity scores appeared approximately continuous and overlaps between the two groups, suggesting that the positivity assumption was not violated. Specifically, we observed that the lower tail of the propensity score distribution does not contain close to zero values in either group. The range of propensity scores for the statin use group was 0.062 to 0.998, with a mean of 0.381, and for the non-use group, the range was 0.062 to 0.935, with a median of 0.207 (shown in Fig. 2).

Statin use was statistically significantly less likely in subjects who developed LC and HCC compared to non-users ($p<0.001$). The prevalence of statin users was lower among patients with LC and HCC compared to those without LC or HCC. Specifically, among patients without LC, 29.1% were statin users, compared to 24.2% of patients with LC. Similarly, among patients without HCC, 33.4% were statin users, compared to 28.5% of patients with HCC. Approximately one-fifth of statin users among those who developed LC (24.2%, N=717) received over 30 cDDD statins from 2003-2013. For the subjects who developed LC exposed to statins, 0<cDDD<30 of statins per year (16.5%, N=489) was the most common, where 30 cDDD statins per year indicate the continuous use of statins for about 2 months per year. Atorvastatin alone was the most frequently used (18.7%, N=541 for subjects who developed LC; 17.5%, N=343 for subjects who developed HCC; Table 2).

In causal inference of statin use on the risk of LC, statin use

Table 1. Baseline characteristics of subjects included on 1 January 2003

		Cirrhosis			Hepatocellular carcinoma		
		Who developed LC	Who did not develop LC	p-value	Who develop HCC	Who did not develop HC	p-value
Total (N (%))		2,964 (5.7)	49,181 (94.3)		1,851 (3.6)	50,294 (96.4)	
Age group (N (%))				<0.001			<0.001
	20~39	594 (20.0)	15,889 (32.3)		401 (21.7)	16,092 (32.0)	
	40~59	1,579 (53.3)	22,181 (45.1)		950 (51.3)	22,810 (45.3)	
	60~	791 (26.7)	11,101 (22.6)		500 (27.0)	11,392 (22.7)	
Sex (N (%))				<0.001			1
	Men	2,030 (68.5)	24,747 (50.3)		1,262 (68.2)	25,515 (50.7)	
	Women	934 (31.5)	24,434 (49.7)		589 (31.8)	24,779 (49.3)	
Comorbidity							
Cardiovascular disease	No	2,714 (91.6)	44,589 (89.3)	<0.001	1,703 (92.0)	45,240 (89.5)	<0.001
	Yes	250 (8.4)	4,592 (10.7)		148 (8.0)	5,054 (10.5)	
Diabetes mellitus	No	2,623 (88.5)	44,772 (91.0)	<0.001	1,653 (89.3)	45,742 (90.9)	<0.001
	Yes	341 (11.5)	4,409 (9.0)		198 (10.7)	4,552 (9.1)	
Hypertension	No	2,209 (74.5)	37,000 (75.2)	<0.001	1,384 (74.8)	37,825 (72.1)	0.021
	Yes	755 (15.3)	12,181 (24.8)		467 (25.2)	12,469 (24.8)	
Cerebrovascular disease	No	2,884 (97.3)	47,519 (96.6)	<0.001	1,798 (97.1)	48,605 (96.4)	0.003
	Yes	80 (2.7)	1,662 (3.4)		53 (13.8)	1,689 (3.6)	
Liver disease							
Hepatitis B virus	No	2,832 (94.5)	46,921 (95.3)	<0.001	1,768 (96.5)	47,985 (95.4)	<0.001
	Yes	132 (5.5)	2,260 (4.6)		83 (3.5)	2,309 (4.6)	
Hepatitis C virus	No	2,902 (97.1)	48,351 (98.3)	<0.001	1,807 (90.6)	49,446 (98.3)	<0.001
	Yes	62 (2.1)	830 (1.7)		44 (2.4)	848 (1.7)	
Other chronic hepatitis	No	2,081 (70.2)	37,654 (76.6)	<0.001	1,320 (71.3)	38,415 (76.4)	<0.001
	Yes	883 (29.8)	11,527 (23.4)		531 (28.7)	11,879 (23.6)	
NAFLD	No	2,640 (89.1)	42,611 (86.6)	<0.001	1,658 (89.6)	43,593 (86.7)	<0.001
	Yes	324 (10.9)	6,570 (13.4)		193 (10.4)	6,701 (13.3)	
Alcoholic liver disease	No	2,366 (79.8)	42,700 (86.8)	<0.001	1,562 (84.4)	43,504 (86.5)	<0.001
	Yes	598 (20.2)	6,481 (13.2)		289 (15.6)	6,790 (13.5)	
Toxic liver disease	No	2,822 (95.1)	46,424 (94.4)	<0.001	1,773 (95.8)	47,473 (94.4)	<0.001
	Yes	142 (4.9)	2,757 (5.6)		78 (4.2)	2,821 (5.6)	
Medication (N (%))							
Anti-diabetic drugs	No	2,608 (88.0)	45,021 (91.5)	<0.001	1,643 (88.8)	45,989 (91.4)	<0.001
	Yes	356 (12.0)	4,157 (8.5)		208 (11.2)	4,305 (8.6)	
Anti-hypertensive drugs	No	2,146 (72.4)	36,014 (73.2)	<0.001	1,346 (72.7)	36,817 (73.2)	<0.001
	Yes	818 (27.6)	13,164 (26.8)		505 (27.3)	13,477 (26.8)	
Lipid-lowering agents (except statin)	No	2,912 (98.2)	48,158 (97.6)	0.035	1,818 (98.2)	49255 (97.9)	0.674
	Yes	52 (1.7)	1,020 (2.4)		33 (1.8)	1,039 (2.1)	

was negatively correlated with the causal estimate of LC by IPW (MOR 0.64, 95% CI 0.57-0.71), and superlearning TMLE (MOR 0.58, 95% CI 0.50-0.65). The estimates of causal inference were similar in HCC by IPW (MOR 0.61, 95% CI 0.53-0.70) and superlearning TMLE (MOR 0.59, 95% CI 0.50-0.67) (Table 3).

As a result of analyzing the causal effect of LC risk according

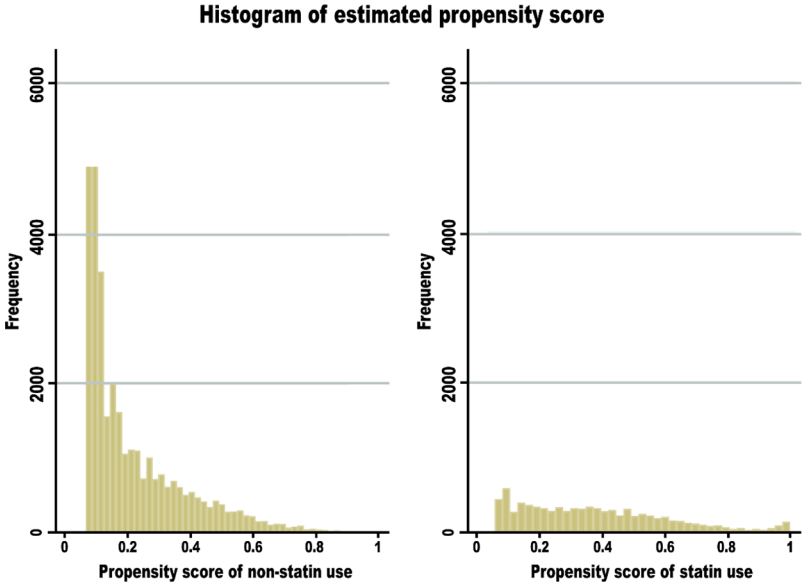

Fig. 2. Histogram of estimated propensity score

to statin dose with superlearning TMLE, the causal estimate decreased greatly when the cumulative dose was ≤720 cDDD (MOR 0.51 95% CI 0.42-0.60) and the yearly dose was 30≤ cDDD<120 (MOR 0.58 95% CI 0.51-0.65). These results were more evident in hydrophilic statin (MOR 0.56 95% CI 0.50-0.62) (Table 4).

In causal inference of atorvastatin on the risk of LC, atorvastatin use was negatively correlated with the causal estimate of LC by IPW (MOR 0.62, 95% CI 0.55-0.69), and superlearning TMLE (MOR 0.58, 95% CI 0.50-0.65). In the riks of HCC, atorvastatin use was negatively correlated with the causal estimate of HCC by IPW (MOR 0.60, 95% CI 0.51-0.69) and superlearning TMLE (MOR 0.59, 95% CI 0.50-0.68). Such statistically significant causal relationship was estimated for atorvastatin, rosuvastatin, simvastatin, and lovastatin. (Table 5).

The superlearning TMLE by subgroup of underlying liver diseases, statin use was estimated to be negatively associated with LC incidence in the patients with hepatitis B (MOR 0.37, 95% CI 0.19-0.55), NAFLD (MOR 0.64, 95% CI 0.46-0.81), other chronic hepatitis (MOR 0.51, 95% CI 0.43-0.58), and alcoholic liver disease (MOR 0.53, 95% CI 0.40-0.65) (Table 6) The results of the sensitivity analyses did not significantly deviate from those of the main analyses (Table 7).

Discussion

In our causal inference analysis, we found the negative causal relationship of statin use on the risk of LC and HCC, as estimated using superlearner TMLE methods. It showed that statin use was significantly associated with a decreased incidence risk of LC, with a MOR of 0.59 and a 95% CI ranging from 0.50 to 0.65. Similarly, for HCC, the MOR was 0.59 with a 95% CI of 0.50 to 0.67. This suggests that statin use effectively reduces the risk of developing LC and HCC. This protective effect was more pronounced with specific types of statins, particularly atorvastatin and lipophilic statins. The consistency of our findings with those obtained using the IPW analysis method enhances the reliability and credibility of the observed causal relationship between statin use and the reduced risk of LC and HCC. This study, therefore, provides better causality supporting the beneficial role of statins in lowering the risk of LC and HCC.

Previous retrospective studies have shown that statin use was associated with a reduction of the risk of LC and HCC.[43,44] However, statins are still not readily recommended for patients with chronic liver diseases to prevent LC or HCC since the causality in this beneficial effect has not been corroborated. Furthermore, conducting a randomized clinical trial on preventive effects against LC and HCC is difficult due to the safety issues of subjects with chronic liver diseases. Therefore, longitudinal, big data with a robust study design is necessary to evaluate causality. The superlearning method improves robustness by minimising bias caused by confounding variables.[45] Our study reinforces the causal relationship between statin use and a lower risk of LC and HCC, aligning with previous research that suggested a correlation between extended statin use and reduced risk of these diseases.

Our study used data from 2002 to 2013, which showed statin

Table 2. Statin administration among the subjects in 2003-2013

		Cirrhosis			Hepatocellular carcinoma		
		Who developed LC	Who did not develop LC	p-value	Who developed HCC	Who did not develop HCC	p-value
Total (N (%))		2,964 (5.7)	49,181 (94.3)		1,851 (3.7)	50,294 (96.3)	
Statin use (N (%))							
	Non-use (cDDD<30)	2,247 (75.8)	34,871 (70.9)	<0.001	1,396 (75.4)	35,722 (71.0)	<0.001
	Use (30≤cDDD)	717 (24.2)	14,310 (29.1.)		455 (24.6)	14,527 (29.0)	
Cumulative dose of statin use				<0.001			<0.001
	cDDD=0	2,120 (71.5)	32,700 (66.5)		1,324 (71.5)	33,496 (66.6)	
	0<cDDD<30	127 (4.3)	2,171 (4.4)		72 (3.9)	2,226 (4.4)	
	30≤cDDD<180	253 (8.5)	4,374 (8.9)		137 (7.4)	4,490 (8.9)	
	180≤cDDD<720	241 (8.1)	5,130 (10.4)		176 (9.5)	5,195 (10.3)	
	720≤cDDD	223 (7.5)	4,806 (9.8)		142 (7.7)	4,887 (9.7)	
Yearly dose of statin				<0.001			<0.001
	cDDD=0	2,120 (71.5)	32,700 (66.5)		1,324 (71.5)	33,496 (66.6)	
	0<cDDD<30	489 (16.5)	8,521 (17.3)		291(15.7)	8,719 (17.3)	
	30≤cDDD<120	264 (8.9)	5,787 (11.8)		178 (9.6)	5,873 (11.7)	
	120≤cDDD	91 (3.1)	2,173 (4.4)		58 (3.1)	2,206 (4.4)	
Statin subclass							
	Atorvastatin	541 (18.7)	11,326 (23.0)	<0.001	343 (17.5)	11,524 (22.9)	<0.001
	Rosuvastatin	119 (4.0)	2,363 (4.8)	0.05	74 (4.0)	2,408 (4.8)	0.117
	Simvastatin	386 (13.0)	7,967 (16.2)	<0.001	257 (13.9)	8,096 (16.1)	0.011
	Pravastatin	238 (4.7)	2,264 (4.6)	0.895	84 (4.5)	2,318 (4.6)	0.887
	Fluvastatin	47 (1.6)	663 (1.4)	0.278	24 (1.2)	686 (1.4)	0.806
	Lovastatin	29 (1.0)	470 (1.0)	0.902	12 (0.7)	487 (1.0)	0.165
	Pitavastatin	80 (2.7)	1,649 (3.4)	0.054	50 (2.7)	1,679 (3.3)	0.133
Statin classification							
	Hydrophilic statin	767 (25.9)	15,274 (31.1)	<0.001	477 (25.8)	15,564 (30.9)	<0.001
	Lipophilic statin	237 (8.0)	4,332 (8.8)	0.129	148 (8.0)	4,421 (8.8)	0.235

Table 3. Causal inference approach of the association of statin use with cirrhosis and hepatocellular carcinoma

Outcome	Statin use (N)	IPW Analysis		Superlearning TMLE	
		†Marginal OR	95%CI	‡Marginal OR	95%CI
Cirrhosis	Non-use (37,118)	1 (Ref)		1 (Ref)	
	Use (15,027)	**0.64****	0.57-0.71	**0.58****	0.50-0.65
Hepatocellular carcinoma	Non-use (37,118)	1 (Ref)		1 (Ref)	
	Use (15,027)	**0.61****	0.53-0.70	**0.59****	0.50-0.67

†Marginal odds ratio for causal inference from inverse probability weighting(IPW) with adjustment for dyslipidemia, cardiovascular disease, high blood pressure, cerebrovascular disease, diabetes mellitus, antihypertensive medication, antidiabetic medication, and lipid-lowering agents (except statin).
‡Marginal odds ratio for causal inference from targeted maximum likelihood estimation (TMLE) with adjustment for dyslipidemia, cardiovascular disease, high blood pressure, cerebrovascular disease, diabetes mellitus, antihypertensive medication, antidiabetic medication, and lipid-lowering agents (except statin).
*p<0.05, **p<0.01

Table 4. Causal inference approach of the association of statin use with cirrhosis and hepatocellular carcinoma according to statin dose

Outcome	Statin dose (N)	Superlearning TMLE	
		Marginal OR‡	95% CI
Cirrhosis	Cumulative dose		
	cDDD<30 (37,118)	1 (Ref)	
	30≤cDDD<180 (4,627)	**0.67***	0.58-0.76
	180≤cDDD<720 (5,371)	**0.56****	0.47-0.65
	720≤cDDD (5,029)	**0.51****	0.42-0.60
	Yearly dose		
	cDDD<10 (37,118)	1 (Ref)	0.69-0.89
	10≤cDDD<30 (3,450)	**0.64****	0.56-0.71
	30≤cDDD<120 (6,044)	**0.58****	0.51-0.65
	120≤cDDD (2,284)	**0.62****	0.54-0.70
	Statin classification		
	Hydrophilic statin (16,401)	**0.56****	0.50-0.62
	Lipophilic statin (4,569)	**0.69****	0.56-0.81
Hepatocellular carcinoma	Cumulative dose		
	cDDD<30 (37,118)	1 (Ref)	0.94-1.06
	30≤cDDD<180 (4,627)	**0.61****	0.51-0.72
	180≤cDDD<720 (5,371)	**0.59***	0.48-0.69
	720≤cDDD (5,029)	**0.52****	0.42-0.63
	Yearly dose		
	cDDD<10 (37,118)	1 (Ref)	
	10≤cDDD<30 (3,450)	**0.62****	0.53-0.72
	30≤cDDD<120 (6,044)	**0.56****	0.47-0.64
	120≤cDDD (2,284)	**0.61****	0.51-0.72
	Statin classification		
	Hydrophilic statin (16,401)	**0.56****	0.47-0.63
	Lipophilic statin (4,569)	**0.70****	0.57-0.83

‡Marginal odds ratio for causal inference from targeted maximum likelihood estimation (TMLE) with adjustment for dyslipidemia, cardiovascular disease, high blood pressure, cerebrovascular disease, diabetes mellitus, antihypertensive medication, antidiabetic medication, and lipid-lowering agents (except statin).
*p<0.05, **p<0.01

use by patients with liver diseases. Thus, we could investigate the effect of statin use on the risk of LC and HCC among patients with liver diseases. A systematic review and meta-analysis of 13 studies similarly revealed that statin users were less likely to develop LC than non-statin users in patients with chronic liver disease without cirrhosis.[43] In another systematic review of 32 studies, statin users were less likely to develop HCC than non-statin users.[44]

The beneficial effect of statin on LC or HCC was supported by preclinical studies, which suggest the mechanism by which statin alleviates liver fibrosis. Statins have anti-inflammation effects,[46] attenuate increased hepatic vascular resistance.[47] Studies have demonstrated that statins elicit antineoplastic effects,[48,49] particularly for atorvastatin.[50] Liver fibrosis due to hepatitis increases the risk of liver cancer. Therefore, the antifibrotic effect of statins may positively affect the pathogenesis of liver cancer and lower its incidence.[49]

This study has several strengths. First, our estimations were based on real-world data from national health insurance claims for all compulsory Korean beneficiaries and all medical providers, including compulsory pharmacists. Therefore, our results are nationally representative, yielding strong generalizability. Second, causality was evaluated using the IPW and TMLE with the super learning method, a robust study design that has not been applied

Table 5. Causal inference approach of the association of statin use with cirrhosis and hepatocellular carcinoma according to statin subclass

Outcome	Statin type (N)	IPW analysis		Superlearning TMLE	
		Marginal OR†	95% CI	Marginal OR†	95% CI
By statin type					
Cirrhosis	atorvastatin (11,867)	**0.62****	0.55-0.69	**0.58****	0.50-0.65
	rosuvastatin (2,482)	**0.60****	0.43-0.77	**0.59****	0.48-0.70
	simvastatin (8,353)	**0.66****	0.57-0.76	**0.63****	0.52-0.71
	lovastatin (499)	**0.64***	0.31-0.98	**0.71****	0.59-0.83
	pravastatin (2,402)	0.89	0.69-1.09	0.83	0.67-1.0
	fluvastatin (710)	1.19	0.64-1.74	0.96	0.82-1.12
	pitavastatin (1,729)	0.80	0.56-1.04	**0.72****	0.57-0.86
Hepatocellular carcinoma	atorvastatin (11,867)	**0.60****	0.51-0.69	**0.59****	0.50-0.68
	rosuvastatin (2,482)	**0.51****	0.37-0.66	**0.62****	0.50-0.74
	simvastatin (8,353)	**0.71****	0.60-0.84	**0.69****	0.56-0.81
	lovastatin (499)	**0.45****	0.13-0.76	**0.55****	0.42-0.68
	pravastatin (2,402)	**0.77***	0.56-0.97	0.82	0.63-1.01
	fluvastatin (710)	0.97	0.45-1.46	0.99	0.80-1.18
	pitavastatin (1,729)	**0.72***	0.45-0.99	**0.68****	0.51-0.86

†Adjusted for dyslipidemia, cardiovascular disease, hypertension, cerebrovascular disease, diabetes mellitus, antihypertensive medication, antidiabetic medication, and lipid-lowering agents (except statin).
*p<0.05, **p<0.01

Table 6. Causal inference approach of the association of statin use with cirrhosis and hepatocellular carcinoma according to underlying liver disease

Outcome	Underlying liver disease (N)	IPW analysis		Superlearning TMLE	
		Marginal OR†	95% CI	Marginal OR†	95% CI
Cirrhosis	Hepatitis B virus (2,392)	**0.39****	0.16-0.59	**0.37****	0.19-0.55
	Hepatitis C virus (892)	-	-	0.95	0.05-1.86
	NAFLD (6,894)	**0.68****	0.50-0.87	**0.64****	0.46-0.81
	Other chronic hepatitis (12,410)	**0.56****	0.48-0.63	**0.51****	0.43-0.58
	Alcoholic liver disease (7,079)	**0.57****	0.44-0.70	**0.53****	0.40-0.65
	Toxic liver disease (2,899)	0.95	0.51-1.39	0.76	0.35-1.17
Hepatocellular carcinoma	Hepatitis B virus (2,392)	**0.51****	0.21-0.82	**0.53****	0.26-0.80
	Hepatitis C virus (892)	-	-	**0.22****	0.02-0.46
	NAFLD (6,894)	**0.64****	0.40-0.88	**0.63****	0.39-0.88
	Other chronic hepatitis (12,410)	**0.52****	0.44-0.61	**0.52****	0.43-0.61
	Alcoholic liver disease (7,079)	**0.73***	0.50-0.96	**0.67****	0.44-0.89
	Toxic liver disease (2,899)	1.04	0.38-1.70	0.98	0.31-1.65

†Adjusted for dyslipidemia, cardiovascular disease, hypertension, cerebrovascular disease, diabetes mellitus, antihypertensive medication, antidiabetic medication, and lipid-lowering agents (except statin).
*p<0.05, **p<0.01

in other studies. The super learning approach in TMLE reduced the chance of misspecifying a model.[51] Third, while previous studies were mainly limited to patients with HBV, HCV, and NAFLD, our study reviewed other chronic liver diseases to determine whether statins affect LC and HCC related to specific underlying liver diseases.[52-54] Similar to previous studies, our study showed that the incidence of LC and HCC decreased amongst statin users with HBV and HCV based on antiviral and

Table 7. Sensitivity analyses of the causal inference approach of the association of statin use with cirrhosis and hepatocellular carcinoma

Outcome	Methods of causal inference	Propensitiy score match		IPW analysis		SuperlearningTMLE	
		§ATE	95%CI	†ATE	95%CI	‡ATE	95%CI
Cirrhosis	Statin use	**-0.022****	-0.028~ -0.015	**-0.023****	-0.028~ -0.017	**-0.028****	-0.0334~ -0.023
	Atorvastatin	**-0.025****	-0.031~ -0.019	**-0.023****	-0.028~ -0.018	**-0.027****	-0.032~ -0.021
Hepatocellular carcinoma	Statin use	**-0.014****	-0.019~ -0.009	**-0.015****	-0.019~ -0.011	**-0.017****	-0.021~ -0.013
	Atorvastatin	**-0.014****	-0.020~ -0.009	**-0.015****	-0.019~ -0.012	**-0.016****	-0.020~ -0.012

§Average treatment effect (ATE) from causal inference of propensity score match analysis, with adjustment for dyslipidemia, cardiovascular disease, high blood pressure, cerebrovascular disease, diabetes mellitus, antihypertensive medication, antidiabetic medication, and lipid-lowering agents (except statin).
†Average treatment effect (ATE) from causal inference of inverse probability weighting anaylsis, with adjustment for dyslipidemia, cardiovascular disease, high blood pressure, cerebrovascular disease, diabetes mellitus, antihypertensive medication, antidiabetic medication, and lipid-lowering agents (except statin).
‡Average treatment effect (ATE) from causal inference of superlearning targeted maximum likelihood estimation, with adjustment for dyslipidemia, cardiovascular disease, high blood pressure, cerebrovascular disease, diabetes mellitus, antihypertensive medication, antidiabetic medication, and lipid-lowering agents (except statin).
*p<0.05, **p<0.01

immunomodulatory effects.[55] Fourth, the study evaluated heterogeneity in the preventive effect of statins on LC and HCC according to the accumulated statin dosage and types. Furthermore, we conducted sensitivity analyses using average treatment effect of propensity score matching, IPW and superlearning TMLE.

Our results should be interpreted with some caution. Our data were obtained from insurance claims, and information on the lifestyles and behavior of patients was lacking. Similarly, data on biochemical examinations, imaging, and biopsies related to liver disease were unavailable; however, we could control many observed and well-described confounders in our adjusted models with such a large cohort.

Conclusion

In conclusion, this population-based observational study indicated that the appropriate use of statin may have negative causal relationship on the incidence risk of LC and HCC. Our causal inference studies suggest that statins may act as disease modifiers in good LC/HCC despite potential adverse events.

Declarations

Data availability

Data described in this study was approved by the Yonsei Institute Review Board (201811-HR-924-02). Further information, including the procedures[56] to obtain and access data from the National Health Insurance Sharing Service is available at https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do (Inquiry telephone; +82-033-736-2453)

Ethics approval and consent to participate

Per Korean law, as this study used completely anonymous data, no ethics approval is required as stated by the Korean Bioethics and Safety Act.[57] Data acquisition and anonymization were performed in accordance with relevant guidelines and local regulations.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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