Association between statin use and the prognosis of hepatocellular carcinoma after resection: a nationwide cohort study

Dongsub Jeon,[a,d] Hye Ryeong Cha,[b,d] Sung Won Chung,[a,d] Jonggi Choi,[a] Danbi Lee,[a] Ju Hyun Shim,[a] Kang Mo Kim,[a] Young-Suk Lim,[a] Han Chu Lee,[a] Seung Won Lee,[c,**] and Won-Mook Choi[a,*]

[a]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b]Department of Computer Science and Engineering, Sungkyunkwan University, Suwon, Gyeonggi-do, Republic of Korea
[c]Department of Precision Medicine, Sungkyunkwan University School of Medicine, Suwon, Gyeonggi-do, Republic of Korea

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Summary

Background The majority of patients with hepatocellular carcinoma (HCC) following hepatic resection experience tumor recurrence. Statin use is associated with a reduced risk of HCC development; however, the association between statin use and the prognosis of HCC after resection remains unclear. We aimed to investigate the effect of statin use on the prognosis after hepatic resection among patients with HCC.

Methods A nationwide cohort study was performed with data from the National Health Insurance Service Database in Korea. Among 65,101 HCC patients who underwent hepatic resection between January 2002 and December 2017, we included 21,470 patients. For validation, a hospital-based cohort of 3366 patients with very early or early-stage HCC who received curative-intent hepatic resection between January 2010 and December 2018 was analyzed. Recurrence-free survival (RFS) and overall survival (OS) was compared between statin users and non-users.

Findings Among the nationwide cohort of 21,470 patients, 2399 (11.2%) used statins and 19,071 (88.8%) did not. Among the hospital cohort of 3366 patients, 363 (10.8%) used statins and 3003 (89.2%) did not. In the propensity score-matched nationwide cohort, statin users had better RFS (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.56–0.64; $P < 0.001$) and OS (HR, 0.49; 95% CI, 0.45–0.53; $P < 0.001$), with a duration-response relationship. In the propensity score-matched validation hospital cohort, statin treatment was significantly associated with better RFS (HR, 0.73; 95% CI, 0.59–0.90; $P = 0.003$) and OS (HR, 0.48; 95% CI, 0.32–0.72; $P < 0.001$). The beneficial effects of statins were more prominent in non-cirrhotics, tumors sized ≥3 cm, tumors with microscopic vascular invasion, or early HCC recurrence (<2 years after resection).

Interpretation Statin use was associated with a better prognosis in a population-based cohort of patients with HCC after hepatic resection, which was further validated in a large hospital-based cohort.

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Keywords: Liver cancer; Lipid-lowering agent; Tertiary prevention; Recurrence-free survival; Overall survival

Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, which is the third leading cause of global cancer-related mortality.[1] By 2040, the global mortality from HCC is expected to double.[2,3] Surgical resection is a potentially curative treatment for HCC in patients with an early stage without extrahepatic metastasis, macrovascular invasion, or clinically significant portal hypertension.[4] However, cumulative recurrence rates are very high even after resection (50%–60%).[5,6] Antiviral treatment reduces the risk of HCC recurrence after hepatic resection in patients with

*Corresponding author. Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Republic of Korea.
**Corresponding author. Department of Precision Medicine, Sungkyunkwan University School of Medicine, 2066, Seobu-ro, Jangan-gu, Suwon, Gyeonggi-do, 16419, Republic of Korea.
E-mail addresses: dr.choi85@gmail.com (W.-M. Choi), swleemd@g.skku.edu (S.W. Lee).
[d]These authors contributed equally to this work.

Research in context

Evidence before this study

We conducted a comprehensive search of PubMed for articles on hepatocellular carcinoma (HCC) prognosis following resection and statin use up to December 31, 2022, yielding 13 relevant articles. Among these, seven studies examined HCC outcomes related to statin use after curative-intent treatment; however, limitations in these studies, including small sample sizes, study design issues, and susceptibility to biases, have hindered firm conclusions. Notably, no national-scale study with minimal selection bias was found to assess the association between statin use and HCC prognosis post-resection.

Added value of this study

In this nationwide, population-based study of patients with HCC who received hepatic resection, statin treatment was associated with a significantly better recurrence-free survival and overall survival compared with no treatment, with a duration-dependent increase in the response. The observed benefit of statins was validated in a hospital cohort of patients with very early or early-stage HCC who received curative-intent resection. Of note, statins were more effective in patients without cirrhosis, tumors larger than or equal to 3 cm in size, tumors with microscopic vascular invasion, and against early HCC recurrence.

Implications of all the available evidence

In a nationwide, population-based cohort study, statin treatment showed promise in enhancing the prognosis of HCC post-hepatic resection. The large treatment effect size observed in the tertiary preventive setting, with a substantial number of events, suggest the feasibility of initiating randomized clinical trials for more robust evidence. These findings on a national scale, less susceptible to bias, could serve as a valuable reference for designing such trials.

chronic hepatitis B[7]; other than antiviral treatment, several trials on sorafenib, interferon α-2b, and vitamin K-2 have been conducted but showed disappointing results.[8–10] Recently, the IMbrave050 study compared atezolizumab plus bevacizumab to active surveillance in HCC patients at high risk of recurrence following curative resection, showing a positive result.[11] However, applying this approach to all resected HCC patients seems challenging due to the high cost and substantial side effects. There is currently no cost-effective and safe method to reduce HCC recurrence, leaving an unmet need for an effective chemopreventive agent.

It has been suggested that statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, could reduce the risk of HCC.[12] Regarding tertiary prevention after curative-intent treatment, a few cohort studies found that statins were associated with a decreased risk of HCC recurrence.[7,13–17] However, there are several limitations in previous studies, such as the small number of study patients (only 31–46 statin users) and the fact that some studies were not designed to evaluate the effects of statins but of other drugs. Moreover, the types of curative treatment included modalities other than resection. Thus, we aimed to investigate the preventive effects of statins on HCC recurrence in patients who received hepatic resection for HCC by using a nationwide population-based cohort and validated the results in a large hospital-based cohort.

Methods

Nationwide cohort

This was a nationwide, population-level, retrospective cohort study of adult patients with HCC who underwent hepatic resection (Appendix Fig. 1A). We analyzed the data accrued in the National Health Insurance Service (NHIS) database of the Republic of Korea. The Korea NHIS database is a comprehensive health database maintained by the Korean government. It encompasses the entire population of South Korea, with 97% covered by the NHIS and the remaining 3% covered under the Medical Aid program. This database contains health-related information, including demographics, medical services, prescriptions, and diagnoses coded with the International Classification of Diseases (ICD) system. Between January 1, 2002, and December 31, 2017 and selected a historical cohort of 42,509 adults with HCC who underwent hepatic resection as the source population with predefined inclusion and exclusion criteria (Fig. 1A). All patients had the ICD-10 code C22 for HCC and the Korea health insurance classification codes for hepatic resection. Patients who met one or more of the following criteria were excluded from the study: younger than 20 years or older than 80 years at baseline; history of treatment for HCC; history of a diagnosis of HIV infection or other cancers; history of decompensation including ascites and variceal bleeding; or history of predefined clinical events (e.g., HCC, liver transplantation, or death of any cause) within 3 months after treatment. Prescription information for aspirin and statins, including the prescribed drug, date filled, days provided, pill number, and dosage, was extracted from the NHIS database using the Anatomical Therapeutic Chemical code (Appendix Table 1). Statin users were defined as patients who had received statin prescriptions within 2 years before and 3 months after the index date and had used statins for a certain period after the index date. Thus, we excluded patients whose last prescription of statins was more than 2 years before the date of resection and those whose first prescription of statins

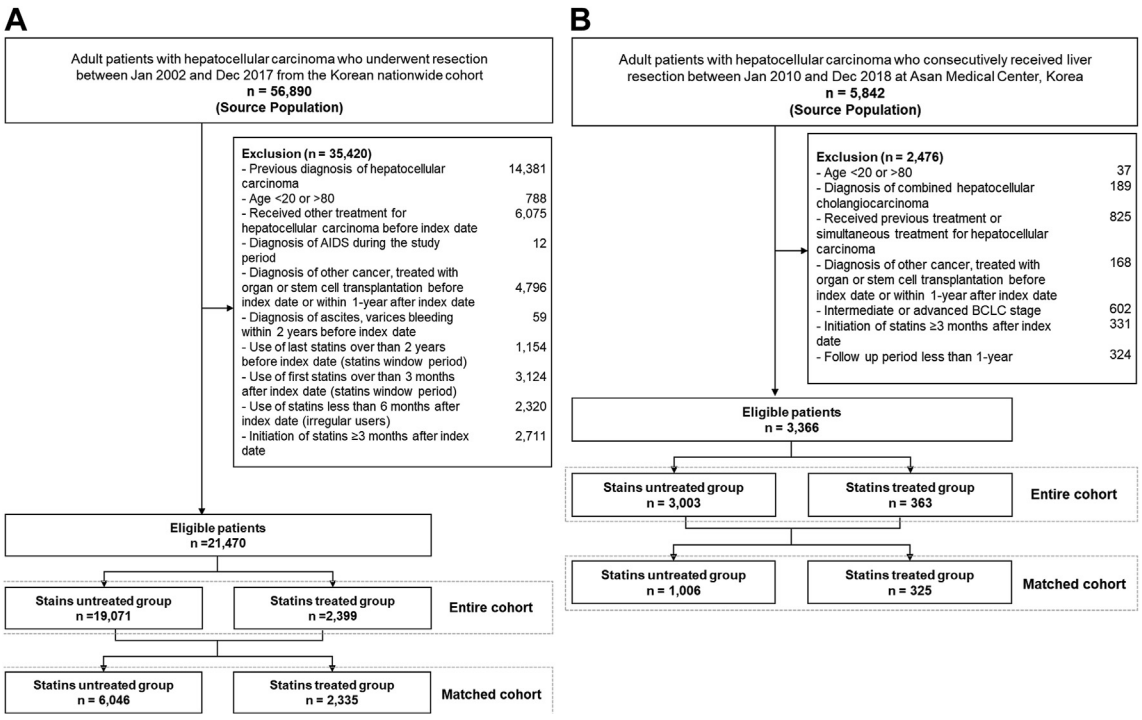

Fig. 1: Patient flow diagram of (A) the nationwide cohort and (B) the validation hospital cohort. AIDS, acquired immunodeficiency syndrome; BCLC, Barcelona Clinic Liver Cancer.

was more than 3 months after resection. To exclude irregular statin users, patients who used statins less than 6 months after hepatic resection were also excluded. All analyses were conducted based on the intention-to-treat principle.

Validation hospital cohort

The NIHS database has limitations in terms of providing detailed individual laboratory data, such as baseline liver function tests and tumor markers, imaging data, and pathological data, which contain important predictors for surgical outcomes of patients with HCC. Therefore, we separately conducted validation analyses using a hospital-based cohort (Appendix Fig. 1B). Adult patients with HCC who consecutively received hepatic resection between January 1, 2010 and December 31, 2018 at Asan Medical Center, a 2700-bed academic tertiary care center in Seoul, Korea, were evaluated for study eligibility. Patients who met one or more of the following criteria were excluded from the study: younger than 20 years or older than 80 years at baseline; history of a diagnosis of combined hepatocellular cholangiocarcinoma; history of treatment or simultaneous treatment for HCC; history of a diagnosis of other cancer or treated with organ or stem cell transplantation; intermediate or advanced stages according to the Barcelona clinical liver cancer staging; initiated statins more than 3 months after hepatic resection; or follow-up duration of less than 1 year. Finally, 363 statin users and 3003 non-users were included in the validation analysis (Fig. 1B).

Ethics

This study was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2020-1650). The board approved a waiver of informed consent from study participants owing to the retrospective nature of the study. The research was conducted in accordance with the Declarations of Helsinki.

Study outcome and covariates

Information on baseline characteristics and clinical outcomes in the nationwide cohort and the validation hospital cohort was collected from the NHIS database based on the relevant diagnostic and procedural codes (Appendix Table 1) and from the electronic medical records of the clinical database of Asan Medical Center, respectively. Cirrhosis and steatosis were assessed based on histological findings in non-tumor tissues obtained from surgical specimens. The primary outcome of interest was recurrence-free survival (RFS) and the secondary outcome was overall survival (OS). The index date was defined as the date of hepatic resection. The operational definition of HCC recurrence in the nationwide cohort was the use of any procedure like radiofrequency ablation, transarterial chemoembolization, radiation

therapy, surgery, or systemic chemotherapy related to HCC after the index date, with the assumption that patients will receive any treatment after HCC recurrence. In the validation hospital cohort, after resection, patients underwent radiological assessments every 2–3 months, with an extension to every 3–6 months if no recurrence was observed for over 2 years. Additional evaluations were conducted based on clinical indications, maintaining a consistent follow-up protocol for both statin users and non-users. Patients were followed up from the index date to the first recorded date of HCC recurrence, death, liver transplantation, or the last follow-up (December 31, 2020 for the nationwide cohort and December 31, 2021 for the validation hospital cohort).

Statistics

Categorical variables are summarized using frequencies and percentages and were compared using the Chi-squared test. Continuous variables are expressed as median and interquartile range or mean and standard deviation and were compared using unpaired two-tailed *t*-tests. Survival outcomes were estimated by the Kaplan–Meier method and compared with the log-rank test. We employed a univariate and multivariable Cox proportional-hazard regression model to evaluate the effect of statins on survival outcomes. Numbers needed to treat was calculated using hazard ratio (HR).[18]

Propensity score (PS)-matching analysis was used to reduce the effect of potential confounding and selection bias between statin users and non-users. Absolute standardized mean differences less than 0.1 between groups after PS-matching were considered to indicate good covariate balance.[19] Since imbalance still exists after PS matching due to intrinsic differences between the two groups, we applied multivariable regression adjustment to remove the residual imbalance. The effects of statins on RFS were also evaluated in predefined subgroups in the PS-matching cohorts. In the validation hospital cohort, missing values ranging from 0.03% to 8.9% of the baseline laboratory data were estimated using multiple imputation. As a sensitivity analysis in the validation hospital cohort to minimize immortal time bias, a landmark analysis was employed to redefine time zero as a specific point, occurring 1 year after the index date. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc) and R statistical software, version 3.6.1 (R Foundation Inc; http://cran.r-project.org/). *P* values less than 0.05 were deemed to indicate statistically significant.

Role of the funding source

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

Baseline characteristics of the nationwide cohort

Among the 21,470 patients included in the nationwide cohort study, 2399 patients were statin users and 19,071 patients were non-users (Fig. 1A). At the time of hepatic resection, the mean age of the study participants was 57.4 years, and 15,940 (74.2%) patients were male. Compared with non-users, statin users were older, had a higher prevalence of various comorbidities including diabetes, hypertension, chronic renal failure, cardiovascular disease, and cerebrovascular disease, and a higher Charlson comorbidity index (all $P < 0.001$; Table 1). Since the baseline characteristics between the two groups were significantly different, we matched statin users with non-users at a 1:4 ratio using PS to minimize the effect of potential confounders in the comparison of surgical outcomes. PS matching generated 2335 statin users and 6046 non-users, and most of the baseline characteristics were well-balanced between the two groups (Table 1).

Clinical outcomes in the nationwide cohort

During a median follow-up period of 34.0 months, 13,432 (62.6%) patients in the PS-matched cohort developed HCC recurrence, received liver transplantation, or died. Statin users showed a significantly better RFS than non-users (HR, 0.60; 95% confidence interval [CI], 0.56–0.64; $P < 0.001$; Fig. 2A), which was consistently observed in the multivariable analyses in both the entire cohort (HR, 0.60; 95% CI, 0.56–0.64; $P < 0.001$; Appendix Table 2) and the PS-matched cohort (HR, 0.60; 95% CI, 0.56–0.64; $P < 0.001$; Table 2) of the nationwide cohort, irrespective of other risk factors. Moreover, a duration-dependent reduction in the risk of HCC recurrence, liver transplant, or death was observed with the cumulative duration of statin treatment. Compared with non-users, the multivariable HRs in statin users were 0.96 (95% CI, 0.86–1.06; $P = 0.40$), 0.48 (95% CI, 0.42–0.54; $P < 0.001$), and 0.37 (95% CI, 0.32–0.42; $P < 0.001$) for patients stratified by increasing tertiles of the cumulative duration of statin treatment. Furthermore, the association between statin treatment and better RFS was observed for both lipophilic statin (HR, 0.60; 95% CI, 0.56–0.65; $P < 0.001$) and hydrophilic statin (HR, 0.59; 95% CI, 0.52–0.67; $P < 0.001$) in multivariable analysis.

In the multivariable Cox proportional-hazard model, statin users showed a significantly lower risk of OS compared with non-users in both the entire cohort (HR, 0.49; 95% CI, 0.49–0.53; $P < 0.001$; Appendix Table 3) and the PS-matched cohort (HR, 0.49; 95% CI, 0.45–0.53; $P < 0.001$; Table 2 and Fig. 2B) of the nationwide cohort, with a duration-dependent risk reduction with multivariable HRs of 0.94 (95% CI, 0.83–1.08; $P = 0.38$), 0.28 (95% CI, 0.23–0.34; $P < 0.001$), and 0.15 (95% CI, 0.13–0.19; $P < 0.001$) for increasing tertiles of the cumulative duration of statin treatment.

Characteristics	Entire cohort			PS-matched cohort (4:1)[a]		
	Untreated (n = 19,071)	Treated (n = 2399)	*P* value	Untreated (n = 6046)	Treated (n = 2335)	SMD
Age, mean ± SD, y	56.6 ± 10.7	64.0 ± 8.7	<0.001	62.3 ± 9.1	63.9 ± 8.7	0.18
Age, n (%)						
<40	1093 (5.7)	17 (0.7)	<0.001	62 (1.0)	16 (0.7)	–
40–49	3682 (19.3)	116 (4.8)		411 (6.8)	114 (4.9)	
50–59	6576 (34.5)	566 (23.6)		1757 (29.1)	554 (23.7)	
≥60	7720 (40.5)	1700 (70.9)		3816 (63.1)	1651 (70.7)	
Male sex, n (%)	14,238 (74.7)	1702 (71.0)	<0.001	4376 (72.4)	1653 (70.8)	0.04
Socioeconomic status, n (%)						
Medical aid (0)	524 (2.8)	126 (5.4)	<0.001	216 (3.6)	121 (5.2)	0.01
Low (1–6)	3727 (19.9)	474 (20.1)		1253 (20.7)	468 (20.0)	
Middle (7–14)	6728 (36.0)	689 (29.2)		2025 (33.5)	679 (29.1)	
High (15–20)	7714 (41.3)	1068 (45.3)		2552 (42.2)	1067 (45.7)	
Etiology, n (%)						
Hepatitis B	11,361 (59.6)	971 (40.5)	<0.001	2790 (46.2)	947 (40.6)	0.12
Hepatitis C	1781 (9.3)	300 (12.5)		782 (12.9)	295 (12.6)	
Others	5929 (31.1)	1128 (47.0)		2474 (40.9)	1093 (46.8)	
Cirrhosis, n (%)	9130 (47.9)	820 (34.2)	<0.001	2402 (39.7)	801 (34.3)	0.11
Aspirin use, n (%)	3785 (19.9)	1661 (69.2)	<0.001	2984 (49.4)	1614 (69.1)	0.46
Antiviral treatment, n (%)	3786 (19.9)	275 (11.5)	<0.001	808 (13.4)	268 (11.5)	0.05
History of diabetes mellitus, n (%)	7958 (41.7)	1965 (81.9)	<0.001	4461 (73.8)	1906 (81.6)	0.18
History of hypertension, n (%)	8049 (42.2)	2125 (88.6)	<0.001	4964 (82.1)	2066 (88.5)	0.15
History of chronic renal failure, n (%)	1281 (6.7)	473 (19.7)	<0.001	765 (12.7)	453 (19.4)	0.20
History of cardiovascular disease, n (%)	781 (4.1)	634 (26.4)	<0.001	652 (10.8)	609 (26.1)	0.45
History of cerebrovascular disease, n (%)	1274 (6.7)	746 (31.1)	<0.001	1025 (17.0)	714 (30.6)	0.37
Charlson comorbidity index, n (%)						
0	3408 (17.9)	98 (4.1)	<0.001	439 (7.3)	96 (4.1)	0.15
1	4588 (24.1)	288 (12.0)		928 (15.3)	283 (12.1)	
≥2	11,075 (58.00)	2013 (83.9)		4679 (77.4)	1956 (83.8)	

Abbreviations: IQR, interquartile range; PS, propensity score; SD, standard deviation; SMD, standardized mean difference. [a]Matched for age, sex, socioeconomic status, etiology, cirrhosis, aspirin use, antiviral treatment, history of diabetes, hypertension, chronic renal failure, cardiovascular disease, cerebrovascular disease, and Charlson comorbidity index.

Table 1: **Baseline characteristics of the patients who underwent resection for hepatocellular carcinoma in the nationwide cohort.**

Both lipophilic (HR, 0.49; 95% CI, 0.44–0.53; $P < 0.001$) and hydrophilic statins (HR, 0.49; 95% CI, 0.41–0.57; $P < 0.001$) were associated with significantly better OS.

Baseline characteristics of the validation hospital cohort

In the validation hospital cohort, the unmatched population included 363 statin users and 3003 non-users (Fig. 1B). The mean age of the unmatched patients was 56.8 years, and 2651 (78.8%) patients were male. Statin users were older, had a higher proportion of patients with aspirin use, diabetes, hypertension, and a lower proportion of those with viral hepatitis and cirrhosis. Platelet counts, international normalized ratio, creatinine, and total cholesterol were also significantly different between the two groups. PS matching yielded a cohort of 1331 patients, which included 325 statin users matched with 1006 non-users. After PS matching, the absolute standardized mean differences of most baseline characteristics were less than 0.1 between groups (Table 3), indicating good covariate balance.

Clinical outcomes in the validation hospital cohort

During a median follow-up duration of 39.9 months, HCC recurrence, death, or liver transplant occurred in 587 (44.1%) of the patients in the PS-matched cohort of the validation hospital cohort. In line with the findings from the nationwide cohort, statin users showed a significantly better RFS (HR, 0.73; 95% CI, 0.59–0.90; $P = 0.003$; Fig. 2C) and OS (HR, 0.48; 95% CI, 0.32–0.72; $P < 0.001$; Fig. 2D) compared with non-users, which was consistently observed in the multivariable Cox proportional-hazard model of the entire cohort and the PS-matched cohort (Table 4 and Appendix Tables 4 and 5). The number needed to treat was 12.5 (95% CI, 7.5–36.4) and 9.3 (95% CI, 5.9–21.9) to prevent one clinical event (i.e., recurrence, liver transplant, or death) at 2 years and 4 years, respectively (Appendix Table 6).

As part of a sensitivity analysis, the 1-year landmark analysis in the PS-matched validation hospital cohort included 1152 patients who did not experience clinical events during the initial 1 year. Most of the baseline characteristics were similar among the patients in the 1-

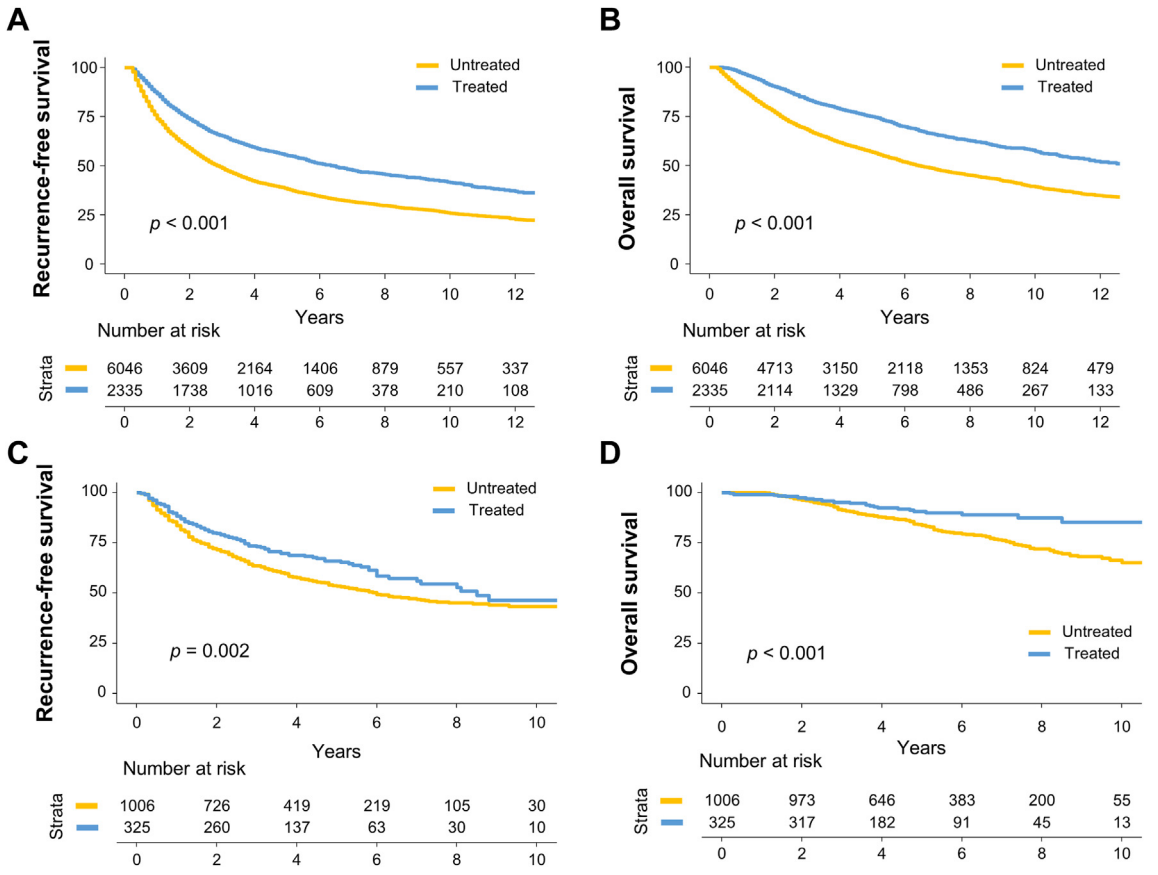

Fig. 2: Kaplan–Meier curves for recurrence-free survival and overall survival in patients who underwent resection for hepatocellular carcinoma. (A) Recurrence-free survival in the propensity score-matched nationwide cohort. (B) Overall survival in the propensity score-matched nationwide cohort. (C) Recurrence-free survival in the propensity score-matched validation hospital cohort. (D) Overall survival in the propensity score-matched validation hospital cohort.

year landmark analysis (Appendix Table 7). Statin users consistently exhibited better RFS (HR, 0.75; 95% CI, 0.59–0.96; P = 0.02) and OS (HR, 0.47; 95% CI, 0.28–0.78; P = 0.004) compared to non-users in the 1-year landmark analysis.

Among the total of 555 patients with HCC recurrence in the validation cohort, 337 (60.7%) and 218 (39.3%) patients had early (<2 years) and late (≥2 years) postoperative recurrences, respectively. Multivariable Cox proportional-hazard model in the PS-matched cohort showed that statin treatment was significantly associated with a lower risk of early recurrence (HR, 0.63; 95% CI, 0.48–0.84; P = 0.002) but not late recurrence (HR, 0.79; 95% CI, 0.56–1.10; P = 0.16) (Appendix Table 8).

Subgroup analyses

In the PS-matched nationwide cohort, statin treatment significantly and consistently improved RFS across all subgroups (Fig. 3A). In the PS-matched validation cohort, the beneficial effect of statins was observed in all subgroups of clinical interest, although statistical significance was not reached in some subgroups due to differences in sample size (Fig. 3B). Of note, the beneficial effect of statins was more prominent in patients without cirrhosis than in those with cirrhosis, in patients with tumors equal to or larger than 3 cm than in those with tumors smaller than 3 cm, and in patients with microscopic vascular invasion than in those without microscopic vascular invasion.

Discussion

In this nationwide, population-based cohort of patients with HCC who underwent hepatic resection, statin use was associated with substantially better RFS and OS. The benefits of statins were duration-dependent, strongly suggesting a potential causal relationship between the exposure and the outcome. Of note, our findings were consistently observed in unadjusted, multivariable-adjusted, and PS-matched analyses and were similar in all predefined subgroups irrespective of

Recurrence-free survival					
Group	No. of patients	No. of events	No. of events/100 patient-years	HR (95% CI)	*P* value
Entire cohort, multivariable-adjusted[a]					
Untreated	19,071	12,261	15.03	Reference	<0.001
Treated	2399	1171	11.03	0.60 (0.56–0.64)	
Propensity score-matched cohort,[b] unadjusted					
Untreated	6046	4136	17.43	Reference	<0.001
Treated	2335	1132	10.93	0.62 (0.58–0.66)	
Propensity score-matched cohort,[b] multivariable-adjusted[c]					
Untreated	6046	4136	17.43	Reference	<0.001
Treated	2335	1132	10.93	0.60 (0.56–0.64)	
Overall survival					
Group	**No. of patients**	**No. of events**	**No. of events/100 patient-years**	**HR (95% CI)**	***P* value**
Entire cohort, multivariable-adjusted[a]					
Untreated	19,071	9011	8.26	Reference	<0.001
Treated	2399	735	5.71	0.49 (0.45–0.53)	
Propensity score-matched cohort,[b] unadjusted					
Untreated	6046	3215	10.20	Reference	<0.001
Treated	2335	711	5.67	0.54 (0.50–0.59)	
Propensity score-matched cohort,[b] multivariable-adjusted[c]					
Untreated	6046	3215	10.20	Reference	<0.001
Treated	2335	711	5.67	0.49 (0.45–0.53)	

Abbreviations: CI, confidence interval; HR, hazard ratio. [a]Adjusted for age, sex, etiology, cirrhosis, aspirin use, antiviral treatment, history of diabetes, hypertension, chronic renal failure, cardiovascular disease, cerebrovascular disease, and Charlson comorbidity index. [b]Matched for age, sex, socioeconomic status, etiology, cirrhosis, aspirin use, antiviral treatment, history of diabetes, hypertension, chronic renal failure, cardiovascular disease, cerebrovascular disease, and Charlson comorbidity index. [c]Adjusted for age, etiology, cirrhosis, aspirin use, history of diabetes, hypertension, chronic renal failure, cardiovascular disease, cerebrovascular disease, and Charlson comorbidity index.

Table 2: **Hazard ratios for recurrence-free survival and overall survival in patients who underwent resection for hepatocellular carcinoma in the nationwide cohort.**

age, sex, etiology of HCC, and comorbidities. These findings were also validated in a large hospital cohort, which showed a similar magnitude of better prognosis in statin users compared with non-users by the same robust statistical methods.

Our study is in line with prior studies that linked statins with better outcomes in patients with HCC after surgical treatment.[7,13–15,17,20,21] However, those studies were limited as they included small numbers of patients (only 31–46 statin users)[13–15] and were not designed to evaluate the effects of statins but of other drugs such as antiviral treatment, antiplatelet therapy, or nonsteroidal anti-inflammatory drugs,[7,13,17,20,21] making it difficult to perform subgroups analysis and evaluate the relative impact of different types of statins (lipophilic vs. hydrophilic) on the prognosis of patients with HCC after resection. In contrast, our study took advantage of an unselected, population-based cohort of patients over a long-term follow-up to generate compelling evidence of a significant, duration-dependent relationship between statin use and the favorable prognosis of HCC after resection. Moreover, the lack of detailed laboratory, imaging, and pathological data, which are the limitations of the claims database, was overcome by validation with a large hospital cohort.

Little is known about the different effects of lipophilic and hydrophilic statins on HCC tertiary prevention and survival. We found similar beneficial effects between lipophilic and hydrophilic statins on the prognosis of HCC. In terms of the secondary prevention of HCC in patients with chronic viral hepatitis, Simon et al. found a lower risk of HCC only with lipophilic statins and not with hydrophilic statins.[22] However, Zou et al. reported a similar risk reduction by both lipophilic and hydrophilic statins in patients with non-alcoholic fatty liver disease.[23] This discrepancy may be attributed to differences in study populations, with the former study focusing on patients with chronic viral hepatitis and the latter study on patients with non-alcoholic fatty liver disease. The lack of a significant difference between lipophilic and hydrophilic statins may be due to the fact that 30%–40% of patients in our study were presumed to have HCC due to non-alcoholic fatty liver disease. Further studies that specifically examine the different effects of lipophilic and hydrophilic statins on HCC tertiary prevention are warranted.

Characteristics	Entire cohort			PS-matched cohort (4:1)[a]		
	Untreated (n = 3003)	Treated (n = 363)	*P* value	Untreated (n = 1006)	Treated (n = 325)	SMD
Demographics						
Age, mean ± SD, y	56.2 ± 9.6	62.2 ± 8.7	<0.001	60.0 ± 9.2	61.7 ± 8.8	0.19
Male sex, n (%)	2356 (78.5)	295 (81.3)	0.24	805 (80.0)	264 (81.2)	0.03
Etiology, n (%)						
Hepatitis B	2355 (78.4)	203 (55.9)	<0.001	645 (64.1)	192 (59.1)	0.20
Hepatitis C	157 (5.2)	14 (3.9)		73 (7.3)	14 (4.3)	
Others	491 (16.4)	146 (40.2)		288 (28.6)	119 (36.6)	
SLD, n (%)	630 (21.0)	137 (37.7)	<0.001	261 (25.9)	117 (36.0)	0.22
Aspirin use, n (%)	78 (2.6)	73 (20.1)	<0.001	69 (6.9)	47 (14.5)	0.25
DM, n (%)	544 (18.1)	179 (49.3)	<0.001	368 (36.6)	148 (45.5)	0.18
Hypertension, n (%)	959 (31.9)	259 (71.3)	<0.001	587 (58.3)	222 (68.3)	0.21
Pathology findings						
BCLC stage, n (%)						
Very early (0)	488 (16.3)	48 (13.2)	0.16	154 (15.3)	46 (14.2)	0.03
Early (A)	2515 (83.7)	315 (86.8)		852 (84.7)	279 (85.8)	
Single tumor, n (%)	2444 (81.4)	295 (81.3)	>0.99	820 (81.5)	267 (82.2)	0.02
HCC size, median (IQR), cm	3.0 (2.1, 4.5)	3.2 (2.3, 5.0)	0.08	3.1 (2.1, 4.8)	3.2 (2.3, 5.0)	0.01
ES grade, n (%)						
I	20 (0.7)	4 (1.1)	0.64	6 (0.6)	3 (0.9)	0.04
II	845 (28.1)	105 (28.9)		292 (29.0)	95 (29.2)	
III	1567 (52.2)	180 (49.6)		505 (50.2)	163 (50.2)	
IV	571 (19.0)	74 (20.4)		203 (20.2)	64 (19.7)	
Microvascular invasion, n (%)	794 (26.4)	91 (25.1)	0.62	254 (25.2)	80 (24.6)	0.02
Capsular invasion, n (%)	245 (8.2)	32 (8.8)	0.74	85 (8.4)	28 (8.6)	0.01
Satellite nodule, n (%)	156 (5.2)	17 (4.7)	0.77	50 (5.0)	17 (5.2)	0.01
Cirrhosis, n (%)	1549 (51.6)	125 (34.4)	<0.001	417 (41.5)	118 (36.3)	0.11
Laboratory findings						
Platelets, median (IQR), × 1000/mm^3	157 (125, 196)	174 (143, 211)	<0.001	165 (131, 203)	174 (143, 209)	0.09
AST, median (IQR), IU/mL	30 (23, 40)	29 (22, 37)	0.05	28 (23, 38)	29 (23, 39)	0.02
ALT, median (IQR), IU/mL	29 (20, 42)	28 (19, 42)	0.04	27 (19, 39)	28 (19, 42)	0.01
Albumin, median (IQR), g/dL	3.8 (3.6, 4.1)	3.9 (3.6, 4.1)	0.49	3.8 (3.6, 4.1)	3.9 (3.6, 4.1)	0.05
Total bilirubin, median (IQR), mg/dL	0.6 (0.5, 0.9)	0.6 (0.4, 0.8)	0.05	0.6 (0.5, 0.9)	0.6 (0.4, 0.9)	0.05
INR, median (IQR)	1.04 (1.00, 1.09)	1.03 (0.99, 1.07)	<0.001	1.03 (0.99, 1.07)	1.03 (0.99, 1.07)	0.05
Creatinine, median (IQR), mg/dL	0.82 (0.71, 0.93)	0.87 (0.76, 1.00)	<0.001	0.83 (0.72, 0.96)	0.86 (0.76, 0.99)	0.14
Total cholesterol, median (IQR), mg/dL	158 (138, 177)	135 (118, 161)	<0.001	150 (133, 167)	137 (120, 161)	0.23
AFP, median (IQR), ng/mL	14.2 (3.9, 161.1)	6.3 (2.7, 56.2)	0.42	9.8 (3.4, 125.7)	6.9 (2.8, 56.4)	0.05
PIVKA-II, median (IQR), mAU/mL	56 (26, 330)	60 (28, 320)	0.85	56 (26, 324)	60 (28, 302)	0.02
Child-Pugh score, median (IQR)	5 (5, 5)	5 (5, 5)	0.16	5 (5, 5)	5 (5, 5)	0.02

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; DM, diabetes mellitus; ES, Edmondson-Steiner; INR, international normalized ratio; IQR, interquartile range; PIVKA-II, prothrombin induced by vitamin K absence-II; PS, propensity score; SD, standard deviation; SLD, steatotic liver disease; SMD, standardized mean difference. [a]Matched for age, sex, diabetes, hypertension, aspirin use, etiology, BCLC stage, platelet counts, levels of INR, total cholesterol, AST, ALT, albumin, bilirubin, AFP, and PIVKA-II, tumor size, tumor number, ES grade, presence of microvascular invasion, capsular invasion, satellite nodules, resection margin involvement, and cirrhosis, and follow-up duration.

Table 3: **Baseline characteristics of the patients who underwent curative resection for hepatocellular carcinoma in the validation cohort.**

In contrast to statins, which have shown a relatively robust effect in previous studies,[7,13–15,17,20,21] including ours, aspirin has displayed conflicting results in previous studies. While some studies found the beneficial effects of aspirin against recurrence after surgical resection for HCC,[7,20,21] others did not.[13,17,24] These discrepancies may be related to differences between the design of each study, including study population, statistical methodology, and the definition of drug exposure. Of note, the effect of aspirin on the primary or secondary prevention of HCC has also been controversial. Indeed, in our previous study, we found that the effect of aspirin on the prevention of HCC may be confounded by statin use in a drug-stratified analysis of CHB patients.[25] Moreover, in the ASPREE trial on healthy elderly individuals, aspirin use resulted in higher cancer-related mortality, including liver cancer, compared to the placebo group.[26] A meta-analysis of

Recurrence-free survival					
Group	No. of patients	No. of events	No. of events/100 patient-years	HR (95% CI)	*P* value
Entire cohort, multivariable-adjusted[a]					
Untreated	3003	1350	10.70	Reference	0.02
Treated	363	133	9.39	0.80 (0.66–0.97)	
Propensity score-matched cohort,[b] unadjusted					
Untreated	1006	471	12.16	Reference	0.002
Treated	325	116	8.99	0.73 (0.60–0.89)	
Propensity score-matched cohort,[b] multivariable-adjusted[c]					
Untreated	1006	471	12.16	Reference	0.003
Treated	325	116	8.99	0.73 (0.59–0.90)	
Overall survival					
Group	**No. of patients**	**No. of events**	**No. of events/100 patient-years**	**HR (95% CI)**	***P* value**
Entire cohort, multivariable-adjusted[a]					
Untreated	3003	502	2.92	Reference	0.004
Treated	363	37	2.09	0.59 (0.41–0.84)	
Propensity score-matched cohort,[b] unadjusted					
Untreated	1006	200	3.69	Reference	<0.001
Treated	325	28	1.76	0.49 (0.33–0.72)	
Propensity score-matched cohort,[b] multivariable-adjusted[c]					
Untreated	1006	200	3.69	Reference	<0.001
Treated	325	28	1.76	0.48 (0.32–0.72)	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ES, Edmondson-Steiner; HR, hazard ratio; INR, international normalized ratio; PIVKA-II, prothrombin induced by vitamin K absence-II. [a]Adjusted for age, sex, diabetes, hypertension, aspirin use, etiology, BCLC stage, platelet counts, levels of AST, albumin, bilirubin, AFP, and PIVKA-II, tumor size, presence of microvascular invasion, capsular invasion, satellite nodules, and cirrhosis. [b]Matched for age, sex, diabetes, hypertension, aspirin use, etiology, BCLC stage, platelet counts, levels of INR, total cholesterol, AST, ALT, albumin, bilirubin, AFP, and PIVKA-II, tumor size, tumor number, ES grade, presence of microvascular invasion, capsular invasion, satellite nodules, resection margin involvement, and cirrhosis, and follow-up duration. [c]Adjusted for age, diabetes, hypertension, aspirin use, etiology, steatotic liver disease, and cirrhosis.

Table 4: **Hazard ratios for recurrence-free survival and overall survival in patients who underwent resection for hepatocellular carcinoma in the validation cohort.**

aspirin prevention trials also indicated a detrimental effect on cancer-related death in individuals aged 70 and older during the initial 3 years of follow-up.[27] Therefore, further robust research may be needed to ascertain aspirin's preventive effects.

In subgroup analyses, we found a consistent beneficial effect of statins on the prognosis of HCC after resection for statins in both the nationwide and the validation cohorts. Of note, the beneficial effect of statins was more predominant in non-cirrhotic patients, those with tumors equal to or larger than 3 cm, or those with tumors with microscopic vascular invasion in the validation cohort. Moreover, although statin treatment was associated with a reduced risk of both early and late HCC recurrence, the magnitude of the risk reduction for early recurrence (HR, 0.63) was greater than that for late recurrence (HR, 0.79). Most cases of early recurrence within 2 years following hepatic resection are considered to be due to the dissemination of the original tumor, whereas most cases of late recurrence after 2 years stem from *de novo* recurrence of tumors developing in the remaining liver.[28–30] Statins limit not just cholesterol production but also other critical downstream products such as membrane integrity, cell signaling, protein synthesis, and cell-cycle progression through the inhibition of the mevalonate pathway, thereby exerting a direct anti-cancer effect.[12,31,32] Moreover, statins may modulate the tumor microenvironment through their anti-inflammatory and antifibrotic effects.[33–36] These preclinical findings, along with the findings of the present study, collectively suggest that the chemopreventive effects of statins may result from the prevention of not only *de novo* tumor recurrence but also primary tumor dissemination in patients with HCC after resection through both direct and indirect anticancer effects. Nevertheless, it is essential to note that previous clinical trials assessing the anticancer effects of statins in advanced HCC have yielded negative results.[37,38] In these previous clinical trials, conducted in the palliative setting with a high tumor burden, as well as in studies like ours, conducted in the adjuvant setting, the tumor biology and microenvironment differ significantly. Consequently, extrapolating the negative outcomes of these clinical trials to the adjuvant setting

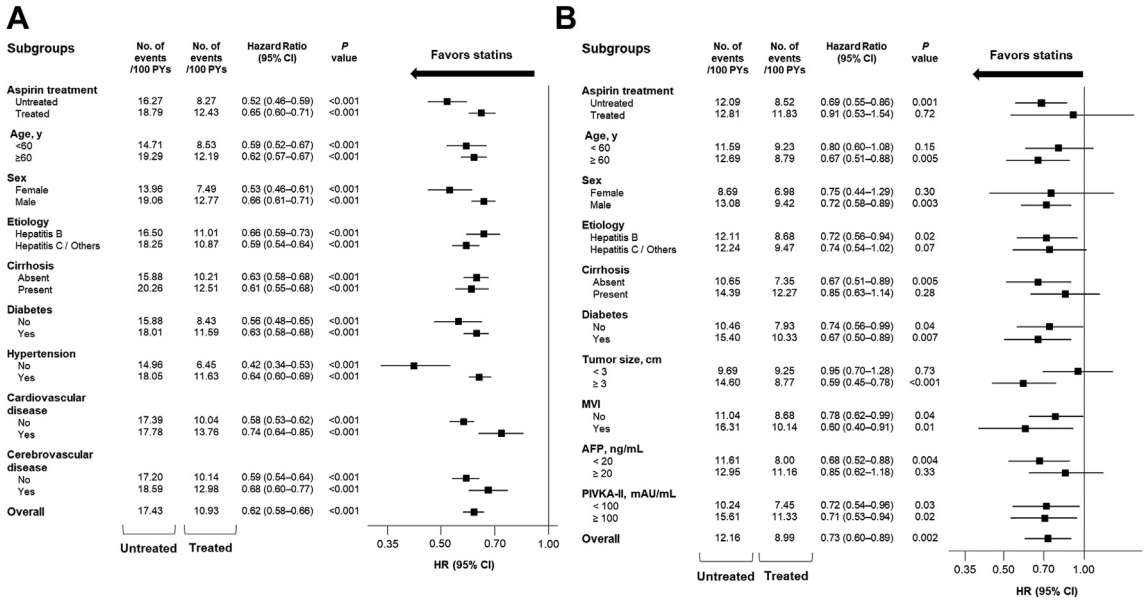

Fig. 3: Subgroup analyses for the association between statin use and recurrence-free survival. Values are presented as HR with 95% CIs. (A) The propensity score-matched nationwide cohort. (B) The propensity score-matched validation hospital cohort. *Adjusted for baseline HBV DNA level and antiviral treatment AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; MVI, microvascular invasion; PIVKA-II, prothrombin induced by vitamin K absence-II; PY, person-year.

presents challenges. To explore the potential anticancer effects of statins in clinical practice, further prospective randomized studies in adjuvant settings are warranted.

Several major limitations of the present study should be noted. First, this nationwide and hospital-based cohort study was based on observational data, which is prone to bias and confounding variables. To overcome this problem, we used multiple strategies (multivariable adjustment and PS matching) to adjust for differences in the baseline characteristics between statin users and non-users. Nevertheless, some imbalance remained even after PS-matching due to intrinsic differences between the two groups, given that statins are primarily prescribed for the primary and secondary prevention of cardiovascular disease. We further applied multivariable regression adjustment to remove residual confounding, which showed a consistent result. Although the two cohorts, the nationwide cohort and the hospital-based cohort, were not entirely independent, our study has a notable advantage that the nationwide cohort and hospital-based cohort complemented each other's shortcomings. The specificity and near-complete follow-up of the Korean NIHS database largely nullified the measurement bias. On the other hand, the lack of detailed laboratory, imaging, and pathological data was supplemented by the hospital-based cohort, both of which yielded very similar results. Second, as hepatitis B virus infection is endemically infected through vertical transmission in South Korea, our findings may be limited in terms of regional generalizability. Our findings should be validated in other regions and ethnicities.

In conclusion, in a nationwide, population-based cohort with patients who received hepatic resection for HCC, statin treatment was associated with significantly better RFS and OS, which was further validated in a large hospital-based cohort. The effects of statins in the primary, secondary, and tertiary preventive settings for HCC have long been an issue. Considering the high number of events and the large treatment effect size of statins in the tertiary preventive setting, the findings of the present study may serve as a basis for conducting randomized clinical trials to provide firm evidence on this issue.

Contributors

SW Lee and W-M Choi conceived the idea of the study. All authors interpreted the findings. D Jeon, HR Cha, and SW Chung contributed to the drafting of the manuscript. J Choi, D Lee, JH Shim, KM Kim, Y-S Lim, and HC Lee contributed to the critical revision of the manuscript for important intellectual content. D Jeon, HR Cha, SW Chung, SW Lee, and W-M Choi performed statistical analysis. W-M Choi obtained funding and provided administrative, technical, or material support. SW Lee and W-M Choi supervised study. SW Lee and W-M Choi have full access to all the data used in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors accept responsibility to submit for publication.

Data sharing statement

NHIS data governance does not allow us to distribute or make available patient data directly to other parties. The code lists used in this study are

provided in the supplementary material. Validation hospital data is available upon reasonable request.

Declaration of interests

There was no funding or support from any industry for this study. The authors are solely responsible for the interpretation and reporting of the data. YS Lim served as advisor for Gilead Sciences and received grant/research support from Gilead Sciences. No other disclosures are declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102300.

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