JHEP|Reports

Statin use and liver-related prognosis among patients with MASLD

Authors

Byungyoon Yun, Heejoo Park, Jian Lee, Beom Kyung Kim, Jin-Ha Yoon

Correspondence

beomkkim@yuhs.ac (B.K. Kim), flyinyou@yuhs.ac (J.-H. Yoon).

Graphical abstract

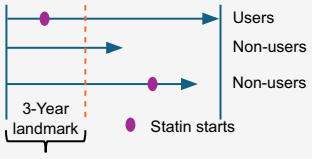
Study population

MASLD participants aged ≥40 with a Fatty Liver Index (FLI) ≥60 in both the 2010-2011 and 2012-2013 health checkups

Primary/secondary outcomes

- Liver-related events (LREs, primary)
- HCC
- Decompensated liver cirrhosis
- All-cause mortality
- Cardiovascular-related mortality
- Liver-related mortality
- Steatotic liver disease (SLD) regression

Definition of statin users

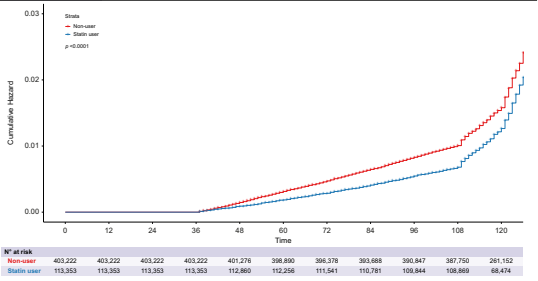


Statistical analysis

- Multivariable Cox models to estimate hazard ratio of LREs and secondary outcomes

Results

Outcome	Statin use	N at risk	Rate§	Adjusted HR
Liver-related events	No	403,222	201.95	Ref (1.00)
	Yes	113,353	164.25	0.64 (0.61-0.68)
All-cause mortality	No	403,977	455.41	Ref (1.00)
	Yes	113,471	494.65	0.81 (0.78-0.83)
HCC	No	403,467	62.78	Ref (1.00)
	Yes	113,380	44.32	0.52 (0.47-0.58)
DLC (including OLT)	No	407,851	47.23	Ref (1.00)
	Yes	113,974	32.18	0.58 (0.52-0.65)
SLD regression	No	400,101	668.54	Ref (1.00)
	Yes	111,192	863.84	1.18 (1.15-1.21)
CVD-related mortality	No	403,977	58.43	Ref (1.00)
	Yes	113,471	69.89	0.87 (0.80-0.95)
Liver-related mortality	No	403,977	48.72	Ref (1.00)
	Yes	113,471	31.87	0.51 (0.46-0.57)



Conclusion

Our study suggests that statin therapy significantly reduces the risk of liver-related events in patients with MASLD/MetALD, highlighting its potential as a preventive strategy

Highlights:

- MASLD is rapidly increasing and contributes to liver and cardiovascular complications.
- Statin use is linked to a reduced risk of liver-related events in patients with MASLD.
- Stratified analyses show greater statin benefits in patients with elevated ALT levels.
- Statin therapy may offer a preventive strategy to improve liver outcomes in MASLD.

Impact and implications:

Our study provides critical evidence supporting the role of statins in reducing liver-related events in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), a condition with significant global health impact. These findings are particularly relevant for clinicians managing high-risk patients with MASLD, especially those with elevated alanine aminotransferase levels, as they highlight the potential for statins to mitigate both liver and cardiovascular risks. By demonstrating the robustness of these results through comprehensive sensitivity and stratified analyses, our research underscores the importance of integrating statin therapy into the management of MASLD. This has practical

https://doi.org/10.1016/j.jhepr.2024.101313

implications for physicians, researchers, and policymakers in developing guidelines and preventive strategies to improve long-term liver and cardiovascular outcomes.

https://doi.org/10.1016/j.jhepr.2024.101313

Research article

JHEP|Reports

Statin use and liver-related prognosis among patients with MASLD

Byungyoon Yun[1,2,3,4], Heejoo Park[5], Jian Lee[5], Beom Kyung Kim[2,6,7,*,†], Jin-Ha Yoon[1,2,3,*,†]

JHEP Reports **2025**. vol. 7 | 1–10

Background & Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a highly prevalent liver condition. We investigated whether statin use reduces liver-related events (LREs) risk among patients with MASLD or MASLD with increased alcohol intake (MetALD).

Methods: This nationwide cohort study included individuals aged ≥40 years with MASLD/MetALD undergoing health examinations between 2012 and 2013. The primary outcome was LREs; hepatocellular carcinoma (HCC), decompensated liver cirrhosis (DLC), and liver-related mortality. Secondary outcomes included HCC, DLC, and steatotic liver disease (SLD) regression, all-cause mortality, cardiovascular diseases (CVD)-related mortality, and liver-related mortality, respectively. Multivariable Cox regression was performed to estimate the risk of LREs associated with statin use.

Results: Among 516,575 individuals (median follow-up: 10.1 years), statin users experienced significantly lower LRE rates (1.6%) compared with non-users (2.0%, p <0.001). Multivariable Cox regression analysis revealed that statin use was associated with reduced risks of LREs (adjusted hazard ratio [aHR] 0.64, 95% CI 0.61–0.68), HCC (aHR 0.52, 95% CI 0.47–0.58), DLC (aHR 0.58, 95% CI 0.52–0.65), all-cause mortality (aHR 0.81, 95% CI 0.78–0.84), CVD-related mortality (aHR 0.87, 95% CI 0.80–0.95), and liver-related mortality (aHR 0.51, 95% CI 0.46–0.57). Furthermore, statin use was associated with SLD regression (aHR 1.18, 95% CI 1.15–1.21). Stratified analyses consistently demonstrated risk reductions across all subgroups, particularly in patients with elevated alanine aminotransferase levels. Sensitivity analyses confirmed the robustness of these associations.

Conclusions: Statins are significantly associated with reduced LRE risk in patients with MASLD, especially among those with elevated alanine aminotransferase levels, suggesting a viable preventive strategy for such population.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), recently introduced as a term to define fatty liver disease,[1–3] is one of the most prevalent liver conditions worldwide, with a rapidly escalating incidence affecting > 30% of the global population. This increase is largely attributable to the widespread occurrence of metabolic syndrome and obesity.[4–6] MASLD encompasses a spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH) with inflammation and fibrosis, accompanied by cardiometabolic components. MASLD is strongly linked not only to an increased risk of liver-related complications,[7] including liver cirrhosis (LC)[1] and hepatocellular carcinoma (HCC)[8,9] but also to an increased cardiovascular disease (CVD) risk,[10] which collectively contribute to a significant reduction in patients' quality of life. Despite extensive efforts to develop effective treatments for MASLD,[11] resmetirom has recently emerged as the only drug conditionally approved by the US Food and Drug Administration for treating patients with metabolic dysfunction-associated steatohepatitis (MASH) moderate-to-severe hepatic fibrosis.[12]

Statins, commonly prescribed as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors to prevent CVDs,[13] are also recognized for their anti-inflammatory and antifibrotic properties, which may help in mitigating the progression of liver fibrosis in patients with MASLD;[14] however, the use of statins in individuals with chronic liver diseases remains limited, primarily because of concerns about potential statin-induced hepatotoxicity and myopathy. Recent studies have highlighted the efficacy of statins in patients with MASLD, including those with LC, showing promising outcomes.[15] As a result, current expert guidelines strongly advocate for the use of statin therapy in patients with MASLD with pre-existing CVD or those at high risk for CVD.[16]

Although the effect of statins on liver-related prognosis in patients with MASLD remains uncertain, recent studies have indicated a significant association between statin use and a

* Corresponding authors. Addresses: Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun–gu, Seoul 03722, Republic of Korea; Tel.: +82 2 2228 1930; fax: +82 2 393 6884 (B.K. Kim); Department of Occupational Health, Department of Preventive Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun–gu, Seoul 03722, Republic of Korea; Tel.: +82 2 2228 5179; fax: +82 2 392 8622 (J-H. Yoon).
E-mail addresses: beomkkim@yuhs.ac (B.K. Kim), flyinyou@yuhs.ac (J.-H. Yoon).
† J.-H Yoon and B.K. Kim contributed equally to this work as co-corresponding authors.
https://doi.org/10.1016/j.jhepr.2024.101313

reduced risk of HCC[17] or liver fibrosis.[18] Given the promising yet inconclusive evidence regarding the effects of statins on liver-related outcomes in patients with MASLD, further research is essential to clarify these associations and assess the potential therapeutic benefits of statins in these individuals.

Therefore, this study aimed to investigate whether statin use reduces the risk of liver-related events (LREs) in patients with MASLD with or without concurrent alcohol consumption, using data from a nationwide cohort in the Republic of Korea. We hypothesized that statin therapy would significantly lower the risk of LREs in these patients.

Patients and methods

Data source and study populations

This new-user cohort study utilized data from the National Health Insurance Service (NHIS), which encompasses more than 97% of the Republic of Korea's population.[19] The NHIS database provides extensive information, including demographic and socioeconomic details, records of outpatient visits and hospitalizations with corresponding diagnostic codes, procedure records, and comprehensive drug prescription information. Additionally, the NHIS systematically conducts biennial comprehensive health checkups for the adult population,[20] which include collecting lifestyle-related data through structured questionnaires and a series of clinical and biochemical assessments. The study included MASLD participants aged ≥40 who participated in a national health checkup between 2012 and 2013. The baseline health examination date was set as the index date for each participant. Patients with MASLD were defined as having steatotic liver disease (SLD) and any cardiometabolic components.[21] SLD was defined as having a Fatty Liver Index (FLI) of ≥60 during both the baseline health checkup conducted in 2012–2013 and the prior health checkup conducted in 2010–2011. An FLI cutoff of 60 is a widely accepted and validated noninvasive test for diagnosing hepatic steatosis,[10] with an area under the receiver operating characteristic (ROC) curve of 0.844. This test exhibits positive predictive values of 83.2% for males and 84.8% for females and negative predictive values of 65.3% for males and 87.4% for females in Asian populations.[22,23]

Cardiometabolic risk factors include the following: (1) a BMI ≥23 kg/m^2 or a waist circumference of ≥90 cm for males and ≥80 cm for females; (2) a fasting glucose level of ≥100 mg/dl, diagnosis of type 2 diabetes, or the use of glucose-lowering medications; (3) blood pressure (BP) of ≥130/85 mmHg or the use of blood pressure-lowering drugs; (4) triglyceride levels of ≥150 mg/dl or the use of lipid-lowering medications; or (5) high-density lipoprotein cholesterol levels <40 mg/dl for males or <50 mg/dl for females, or the use of lipid-lowering drugs.

Among individuals with both SLD and at least one cardiometabolic risk factor, those who reported moderate alcohol consumption (weekly intake of 210–420 g for males and 140–350 g for females) were classified as MetALD, indicating 'MASLD with increased alcohol intake'. In contrast, those who reported a weekly alcohol intake of <210 g for males and <140 g for females were classified as having MASLD.

The exclusion criteria for the study were as follows: (1) missing values for residential area or household income; (2) missing values for measurement, blood test, or lifestyle questionnaires; (3) any history of statin prescription before the index date; (4) history of concurrent liver disease including viral hepatitis (B15–B19), toxic liver disease (K71), biliary cholangitis (K74.3–K74.5), autoimmune hepatitis (K75.4), Wilson's disease (E83.0), and hemochromatosis (E83.1); (5) history of HCC; (6) history of any CVD; (7) history of any types of malignancies excluding HCC; (8) history of decompensated liver cirrhosis (DLC) and orthotopic liver transplantation (OLT); (9) SLD without any component of cardiometabolic criteria; (10) history of alcoholic liver disease or severe alcohol consumption (≥420 g/week for males and ≥350 g/week for females); and (11) patients who developed LREs within the landmark period of 3 years from the index date. Disease and drug prescriptions were evaluated based on insurance claims data during the 2-year lookback period from the index date.

This study adhered to the ethical principles of the Declaration of Helsinki and Istanbul and was approved by the Institutional Review Board (IRB) of Severance Hospital (IRB number: 4-2024-0398). The need for informed consent was waived because of the retrospective nature of this study.

Main outcomes

The primary outcome was the incidence of LREs, including newly developed HCC, DLC (including OLT), or liver-related mortality. The date of HCC diagnosis was determined based on the earliest recorded hospital visit with the International Classification of Diseases 10th Revision (ICD-10) code C220 and the 'V193' code. This was part of a registration program initiated by the government of the Republic of Korea in 2006 to reduce co-payments for rare and intractable diseases.[24] DLC was identified using ICD-10 codes associated with decompensated events, in conjunction with relevant procedural codes. The secondary outcomes included HCC, DLC (including OLT), all-cause mortality, CVD-related mortality, liver-related mortality, and SLD regression. SLD regression was defined as a decrease in the FLI score to below 30 at follow-up, starting from a baseline score of ≥60.[25] The participants were followed until they developed LREs, died, or died in December 2022, whichever occurred earlier. The disease and cause of death definitions used in this study are summarized in Table S1.

Statin exposure

All patients who received statin prescriptions during the observation period were identified. The prescribed statins included atorvastatin, rosuvastatin, pravastatin, fluvastatin, simvastatin, lovastatin, and pitavastatin. Statin use was defined as a prescription of statin for ≥90 days during the follow-up period.[26] A statin user was defined based on the 3-year landmark period utilized in the primary analysis. Patients who received an initial statin prescription within 3 years of the index date were categorized as statin users. In contrast, those who were either never prescribed statins or received a prescription beyond the 3-year period were categorized as non-users.

Covariates

Age, sex, household income quartile, residential area (Seoul *vs.* urban *vs.* rural), smoking history, alcohol intake, physical activity, hypertension, diabetes, LC, and abnormal alanine aminotransferase (ALT) were used as covariates. Factors

associated with FLI estimation were excluded from the analysis.

Individuals were classified as non-smokers, ex-smokers, or current smokers based on lifestyle questionnaires. Increased alcohol intake was defined as a weekly alcohol intake of 210 to <420 g for males and 140 to <350 g for females, based on the definitions of MASLD and MetALD, respectively. For physical activity, the metabolic equivalent of tasks (MET-hours/week) for each participant was calculated based on the sum of the history of vigorous (7 METs) and moderate (4 METs) physical activity and walking (2.9 METs).[27] The participants' physical activity was categorized into four groups: 0–499, 500–999, 1,000–1,499, and ≥1,500 MET-min/week.[28] Hypertension was defined as prescribing antihypertensive drugs with ICD-10 code I10–13, I15, systolic BP ≥140 mmHg, or diastolic BP ≥90 mmHg. Type 2 diabetes was defined as a prescription of antidiabetic drugs with ICD-10 code E11-14 or FBS ≥126 mg/dl. LC was also defined based on related ICD-10 codes, which are summarized in Table S1. We classified participants into two groups based on serum ALT levels: normal (ALT <34 U/L for males, <25 U/L for females) and elevated (ALT ≥34 U/L for males, ≥25 U/L for females).[29]

Statistical analysis

The baseline characteristics of the participants stratified by statin users and non-users are presented as median (IQR) or n (%), as applicable. The cumulative incidence rates of LREs and secondary outcomes were estimated using the Kaplan–Meier method and compared using the log-rank test. The adjusted hazard ratios (aHRs) and 95% CIs of the primary and secondary outcomes were estimated using multivariate Cox proportional hazards models. To validate the results, three models were generated: (1) Model 1 was adjusted for age and sex; (2) Model 2 was adjusted for age, sex, residential area, household income, smoking history, alcohol consumption, and physical activity; and (3) the Final model was adjusted for hypertension, diabetes, LC, abnormal ALT levels, and the variables included in Model 2.

Stratified analyses were conducted according to age, sex, hypertension, diabetes, BMI, and abnormal ALT levels to evaluate the risk of LREs associated with statin use. Additionally, several sensitivity analyses were performed: (1) medications related to hypertension or diabetes, such as angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), non-selective and selective beta-blockers (BBs), calcium channel blockers (CCBs), diuretics and other antihypertensive drugs, dipeptidyl peptidase-4 inhibitor (DPP4i), metformin, sulfonylurea (SU), thiazolidinedione (TZD), alpha-glucosidase, and other oral antidiabetic drugs were adjusted. These variables were generated based on whether they were taken for more than 90 days in the 2 years before the index date; (2) different landmark periods (1, 2, 4–5 years) were used to define statin users; (3) time-dependent Cox regression was applied to treat statin use as a time-varying variable to reduce immortal time bias; (4) propensity score matching and inverse probability of treatment weighting were used to mitigate confounding bias; (5) Fine and Gray regression was utilized by considering all-cause mortality as a competing risk; (6) to account for the potential influence of frequent healthcare utilization among statin users, the analysis was further adjusted for the number of hospital visits within 2 years before the index date (<12, 12–23, ≥24); (7) the impact of statin use on SLD regression was assessed. Propensity score matching (PSM) was performed using a ratio of 1:1 with a greedy caliper width of 0.05, and the standardized mean difference (SMD) was used to assess the balance of variables. All statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc., Cary, NC, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). All results were considered significant if the 95% CI did not include 1.

Results

Baseline characteristics of participants

Of the 898,939 individuals who had SLD on two occasions during health examinations in 2010–2011 and 2012–2013, 516,575 individuals were included in the final analysis after applying the exclusion criteria (Fig. 1). The median participant age was 50 years (IQR, 44–52 years), and 84.4% of the participants were male. The proportion of participants using statins was 21.7% (n = 113,353). Based on baseline characteristics (Table 1), statin users were more likely to be older, female, and non-smokers, with lower alcohol consumption and a higher prevalence of hypertension, diabetes, and use of other antihypertensive or antidiabetic medications (all p <0.001).

Cumulative incidence and the risk of primary and secondary outcomes associated with statin use among patients with MASLD and/or alcohol intake

During the median follow-up period of 10.2 years, 9,910 (1.9%) patients developed LREs: 2.0% (n = 8,069) non-users and 1.6% (n = 1,841) statin users. The 10-year cumulative incidence rates of LREs in the non-user and statin-user groups were 1.7% and 1.3%, respectively (p <0.001; Fig. 2). Secondary outcomes were as follows: all-cause mortality, 23,811 (4.6%); HCC, 3,008 (0.6%); DLC, 2,304 (0.4%); CVD-related mortality, 3,127 (0.6%); liver-related mortality, 2,311 (0.4%); and SLD regression, 35,630 (6.8 %). The 10-year cumulative incidence rates of secondary outcomes were 4.5%, 0.6%, 0.5%, 0.6%, 0.5%, and 6.3% for all-cause mortality, HCC, DLC, CVD-related mortality, liver-related mortality, and SLD regression, respectively, among non-users compared with 5.2%, 0.5%, 0.3%, 0.7%, 0.3%, and 8.2% among statin users (p <0.001).

Multivariable Cox proportional hazards analysis in Table 2 revealed that statin use was significantly associated with a reduced risk of LREs (aHR 0.64, 95% CI 0.61–0.68), as well as decreased risk of all-cause mortality (aHR 0.81, 95% CI 0.78–0.83), HCC (aHR 0.52, 95% CI 0.47–0.58), DLC (aHR 0.58, 95% CI 0.52–0.65), CVD-related mortality (aHR 0.87, 95% CI 0.81–0.95), liver-related mortality (aHR 0.51, 95% CI 0.46–0.57), and enhanced regression of SLD (aHR 1.18, 95% CI 1.15–1.21), according to the Final model.

Stratification analysis for the risk of LREs associated with statin use among patients with MASLD and/or alcohol intake

Stratification analyses (Table 3) revealed a significant association between statin use and a reduced risk of LREs across all stratified groups, with an approximate 30–40% reduction in LRE risk.

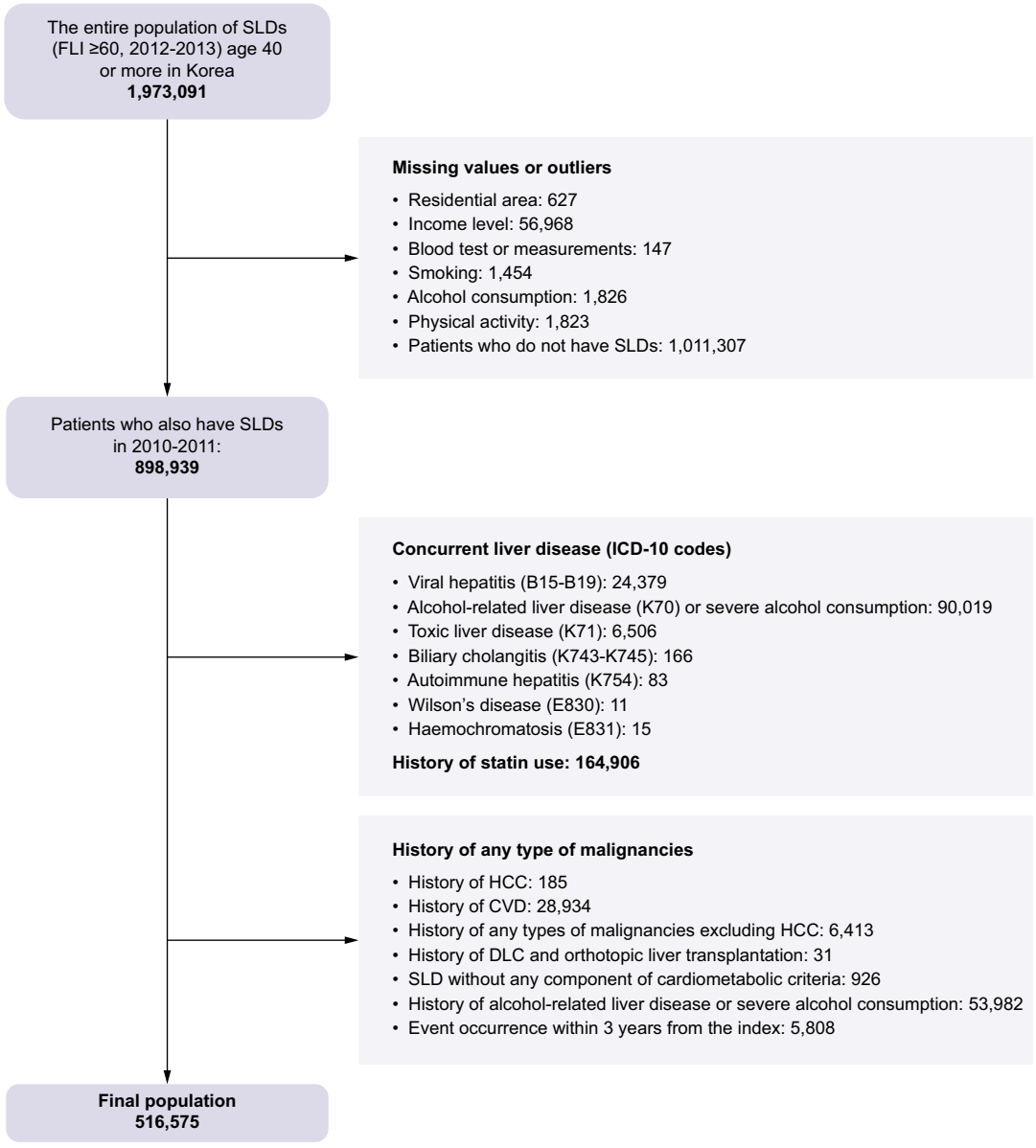


Fig 1. Flowchart of the participant selection process. CVD, cardiovascular disease; DLC, decompensated liver cirrhosis; FLI, Fatty Liver Index; HCC, hepatocellular carcinoma; ICD-10, International Classification of Diseases 10th Revision; SLD, steatotic liver disease.

Patients with elevated ALT levels exhibited a pronounced effect of statin use in reducing the risk of LREs, whereas risk reduction in patients with normal ALT levels was minimal. In other subgroups, such as those stratified by age, sex, hypertension, diabetes, LC, and obesity, the extent of LRE risk reduction associated with statin use was relatively consistent.

Sensitivity analyses for the risk of LREs associated with statin use among patients with MASLD and/or alcohol intake

We conducted several sensitivity analyses. First, the risk of LREs remained significantly reduced with statin use, even after adjusting for various antihypertensive medications (ACEi or ARB, non-selective and selective BB, CCB, and others) and oral antidiabetic drugs (TZD, metformin, SU, DPP4i, and others), yielding an aHR of 0.64 (95% CI 0.61–0.68). Second, the decreased risk of LREs associated with statin use was consistently significant across different landmark periods (1, 2, and 4–5 years, as shown in Table S2). Third, following PSM, the baseline characteristics between the two groups were well-balanced, with absolute SMD <0.1 (Table S3). The primary analysis of the PSM cohort similarly demonstrated a significantly reduced risk of LREs with statin use (aHR 0.83, 95% CI 0.78–0.88, Table S4). Fourth, analyses using time-dependent Cox models, inverse probability weighting (IPTW) Cox models, and Fine-Gray Regression analysis further confirmed this significant association (Table S4). Fifth, even after adjusting for healthcare utilization, statin use remained significantly associated with a reduced risk of LREs (aHR 0.65, 95% CI 0.62–0.68). Last, when we categorized participants into three subgroups according to dose of consistent alcohol

Table 1. Baseline characteristics of participants by statin use.

	Non-user (n = 403,222)	Statin user (n = 113,353)
Age, years (range)	50 (44–57)	53 (46–60)
Sex		
Male	352,970 (87.54)	88,072 (77.7)
Female	56,849 (13.03)	25,281 (22.3)
Residential area		
Seoul	72,658 (18.02)	20,189 (17.81)
Urban	102,870 (25.51)	29,631 (26.14)
Rural	227,694 (56.47)	63,533 (56.05)
Household income		
High	101,828 (25.25)	27,700 (24.44)
High-middle	103,201 (25.59)	26,496 (23.37)
Low-middle	100,549 (24.94)	28,323 (24.99)
Low	97,644 (24.22)	30,834 (27.2)
Smoking		
None	130,385 (32.34)	44,885 (39.6)
Ex-smoker	106,885 (26.51)	29,180 (25.74)
Current smoker	165,952 (41.16)	39,288 (34.66)
Alcohol consumption		
Low (<210 g/week for male and <140 g/week for female)	317,674 (78.78)	92,610 (81.7)
High (210 g to <420 g/week for male and 140 g to <350 g/week for female)	85,548 (21.22)	20,743 (18.3)
Physical activity (METs–min/week)		
≥1,500	20,012 (4.96)	5,748 (5.07)
1,000–1,499	46,159 (11.45)	12,255 (10.81)
500–999	119,213 (29.57)	31,821 (28.07)
<500	217,838 (54.02)	63,529 (56.05)
Hypertension		
No	212,457 (52.69)	34,958 (30.84)
Yes	190,765 (47.31)	78,395 (69.16)
Diabetes		
No	327,219 (81.15)	67,478 (59.53)
Yes	76,003 (18.85)	45,875 (40.47)
Abnormal alanine transaminase*		
No	186,499 (46.25)	49,855 (43.98)
Yes	216,723 (53.75)	63,498 (56.02)
LC		
No	400,004 (99.2)	112,475 (99.23)
Yes	3,218 (0.8)	878 (0.77)
Non-selective beta-blocker		
No	395,673 (98.13)	109,798 (96.86)
Yes	7,549 (1.87)	3,555 (3.14)
Selective beta-blocker		
No	385,206 (95.53)	105,287 (92.88)
Yes	18,016 (4.47)	8,066 (7.12)
Angiotensin receptor blocker		
No	330,606 (81.99)	80,321 (70.86)
Yes	72,616 (18.01)	33,032 (29.14)
Calcium channel blocker		
No	333,251 (82.65)	82,603 (72.87)
Yes	69,971 (17.35)	30,750 (27.13)
Diuretics (and others)		
No	353,260 (87.61)	90,336 (79.69)
Yes	49,962 (12.39)	23,017 (20.31)
DPP4-inhibitor		
No	396,847 (98.42)	109,169 (96.31)
Yes	6,375 (1.58)	4,184 (3.69)
Metformin		
No	379,900 (94.22)	98,997 (87.34)
Yes	23,322 (5.78)	14,356 (12.66)
Sulfonylurea		
No	383,591 (95.13)	101,390 (89.45)
Yes	19,631 (4.87)	11,963 (10.55)
Thiazolidinedione		
No	401,255 (99.51)	112,035 (98.84)
Yes	1,967 (0.49)	1,318 (1.16)
Alpha-glucosidase (and others)		
No	399,535 (99.09)	111,020 (97.94)

(*continued on next page*)

Table 1. (*continued*)

	Non-user (n = 403,222)	Statin user (n = 113,353)
Yes	3,687 (0.91)	2,333 (2.06)
Body mass Index (kg/m^2)	27.8 (26.1–29.7)	27.8 (26.1–29.7)
Waist circumference (cm)	92 (88–97)	92 (88–97)
Systolic blood pressure (mmHg)	130 (120–138)	130 (120–138)
diastolic blood pressure (mmHg)	80 (76–88)	80 (76–88)
Fasting blood glucose (mg/dl)	101 (93–114)	101 (93–114)
GGT (IU/L)	67 (43–109)	67 (43–109)
Aspartate transaminase (U/L)	28 (23–37)	28 (23–37)
Alanine aminotransferase (U/L)	34 (25–48)	34 (25–48)
Total cholesterol (mg/dl)	206 (185–230)	228 (204–254)

consumption (MASLD [consumption <210 g/week for males and <140 g/week for females], MetALD with low-dose alcohol [210 to <280 g/week for males and 140 to <210 g/week for females], and MetALD with high-dose alcohol [280 to <420 g/week for males and 210 to <350 g/week for females]), the significant association between statin use and SLD regression in all subgroups was maintained (Table S5).

Discussion

Our new-user cohort study demonstrated a significant association between statin use and a reduced risk of LREs in patients with MASLD/MetALD, even after adjusting for various covariates, including demographic characteristics, metabolic factors, and lifestyle variables. In secondary analyses, statin use was also significantly associated with a lower risk of HCC, LC with/without decompensation, all-cause mortality, CVD-related mortality, liver-related mortality, and an increased likelihood of FLI regression. These findings were consistent across all sensitivity analyses. While it is challenging to fully disentangle the contributions of each factor within the current dataset, the inclusion of both CVD-related and liver-related mortality outcomes strengthens the plausibility that statins confer benefits across multiple domains.

Previous studies have also demonstrated a positive association between statin use and favorable liver prognosis in patients with non-alcoholic fatty liver disease (NAFLD). In terms of HCC, For instance, Zou *et al.*[17] found that new statin users had a 53% reduced risk of developing HCC among patients with NAFLD, as observed in the Optum de-identified Clinformatics database, a finding that aligns with the extent of risk reduction reported in our study. In terms of LREs, a recent multi-center cohort study found that statin use has a favorable impact on long-term liver-related outcomes (HR 0.38; 95% CI 0.27–0.54) and liver stiffness progression (HR 0.54; 95% CI 0.39–0.76).[18] Our findings are consistent with these previous studies, further supporting the beneficial effects of statins on liver-related outcomes. Furthermore, our study found that statin use had a favorable effect on the regression of SLD.

Although previous studies focused on the lipid-lowering properties of statins, emerging evidence support their multifaceted

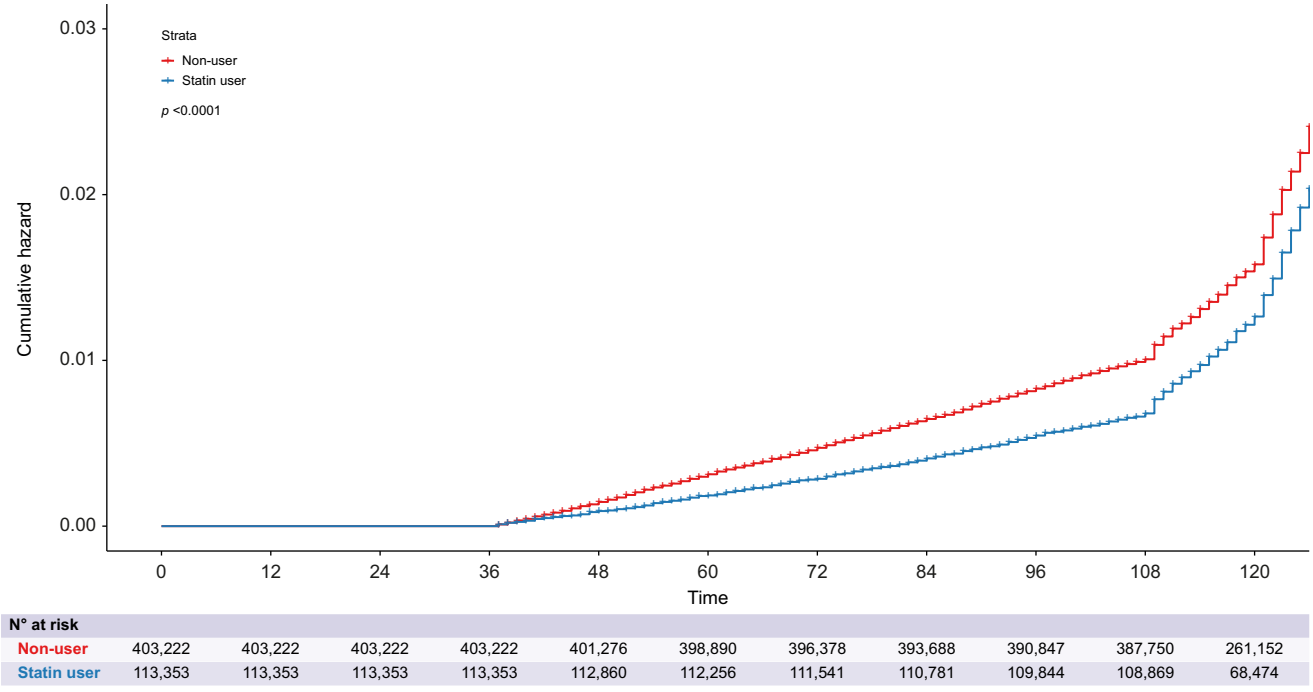


Fig 2. Cumulative incidence plot of liver-related events by statin use among patients with MASLD/MetALD. MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol intake.

Table 2. Multivariable Cox proportional hazards models for liver-related events among patients with MASLD/MetALD.

Outcome	Statin	At risk, n	Events, n	Rate*	Crude model	Model 1	Model 2	Final model
Liver-related events	Non-user	403,222	8,069	201.947	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
	Statin user	113,353	1,841	164.249	0.81 (0.77–0.86)	0.70 (0.66–0.73)	0.70 (0.66–0.74)	0.64 (0.61–0.68)
All-cause mortality	Non-user	403,977	18,255	455.41	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
	Statin user	113,471	5,556	494.652	1.09 (1.06–1.12)	0.87 (0.84–0.89)	0.87 (0.84–0.89)	0.81 (0.78–0.83)
HCC	Non-user	403,467	2,511	62.782	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
	Statin user	113,380	497	44.316	0.71 (0.64–0.78)	0.60 (0.54–0.66)	0.60 (0.54–0.66)	0.52 (0.47–0.58)
DLC (including OLT)	Non-user	407,851	1,936	47.228	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
	Statin user	113,974	368	32.179	0.68 (0.61–0.76)	0.60 (0.54–0.67)	0.6 (0.54–0.67)	0.58 (0.52–0.65)
SLD regression	Non-user	400,101	26,280	668.538	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
	Statin user	111,192	9,350	863.844	1.30 (1.27–1.33)	1.28 (1.25–1.32)	1.28 (1.25–1.31)	1.18 (1.15–1.21)
CVD-related mortality	Non-user	403,977	2,342	58.426	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
	Statin user	113,471	785	69.889	1.20 (1.11–1.30)	0.95 (0.88–1.03)	0.95 (0.88–1.03)	0.87 (0.80–0.95)
Liver-related mortality	Non-user	403,977	1,953	48.722	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
	Statin user	113,471	358	31.873	0.66 (0.59–0.73)	0.54 (0.48–0.60)	0.54 (0.48–0.60)	0.51 (0.46–0.57)

Model 1 was adjusted for age, and sex. Model 2 was adjusted for age, sex, residential area, household income, smoking, alcohol consumption, and physical activity. The Final model was adjusted for adjusted for age, sex, residential area, household income, smoking, alcohol consumption, physical activity, hypertension, diabetes, LC, and abnormal alanine transaminase.

CVD, cardiovascular disease; DLC, decompensated liver cirrhosis; HCC, hepatocellular carcinoma; LC, liver cirrhosis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol intake; OLT, orthotopic liver transplantation; SLD, steatotic liver disease.

*Rates are expressed per 100,000 person-years.

benefits on liver health through pleiotropic mechanisms. One key mechanism involves upregulation of Kruppel-like factor 2 (KLF2), a crucial transcription factor in hepatic endothelium, affecting inflammation, fibrosis, apoptosis, oxidative stress, vasodilation, and thrombus formation.[30] Through the Rac1–MEK5–ERK5–MEF2 pathway, statins enhance KLF2 expression, leading to hepatic stellate cell (HSC) deactivation and inhibition of their migration and proliferation.[31,32] Additionally, statins inhibit the Ras homolog gene family member A (RhoA)/Rho-kinase pathway, reducing HSC contraction by activating myosin light-chain phosphatase and decreasing phosphorylated myosin levels. These mechanisms collectively improve hepatic perfusion by lowering hepatic venous resistance and portal pressure, which ultimately enhances liver function.[33] Experimental models have also demonstrated that inhibiting HMG-CoA reductase and its downstream products, such as geranylgeranyl pyrophosphate, can regulate angiogenesis, cell proliferation, cell cycle progression, and metastasis, while also promoting apoptosis.[34] Additionally, a

Table 3. Stratified analyses of the association between statin use and the risk of liver-related events.

Variable		Statin	At risk, n	Events, n	Rate*	Adjusted HR (95% CI)
Age group	40-64	Non-user	361,231	5,940	165.03	Reference (1.00)
		Statin user	96,018	1,287	134.69	0.64 (0.60–0.68)
	≥65	Non-user	41,991	2,129	537.23	Reference (1.00)
		Statin user	17,335	554	335.05	0.63 (0.57–0.70)
Sex	Male	Non-user	352,970	6,734	192.27	Reference (1.00)
		Statin user	50,252	1,335	270.63	0.66 (0.62–0.70)
	Female	Non-user	88,072	1,407	161.39	Reference (1.00)
		Statin user	25,281	434	174.27	0.6 (0.53–0.67)
Hypertension	No	Non-user	212,457	3,230	152.55	Reference (1.00)
		Statin user	34,958	480	138.09	0.64 (0.58–0.71)
	Yes	Non-user	190,765	4,839	257.64	Reference (1.00)
		Statin user	78,395	1,361	176.01	0.63 (0.59–0.67)
Diabetes	No	Non-user	327,219	5,246	161.22	Reference (1.00)
		Statin user	76,003	2,823	380.61	0.7 (0.65–0.76)
	Yes	Non-user	67,478	885	132.02	Reference (1.00)
		Statin user	45,875	956	212.2	0.59 (0.55–0.63)
LC	No	Non-user	400,004	6,205	156.36	Reference (1.00)
		Statin user	112,475	1,424	127.96	0.62 (0.59–0.66)
	Yes	Non-user	3,218	1,864	6,832.16	Reference (1.00)
		Statin user	878	417	5,196.42	0.68 (0.61–0.76)
BMI	<25	Non-user	49,433	2,200	453.94	Reference (1.00)
		Statin user	12,695	405	323.49	0.57 (0.51–0.64)
	≥25	Non-user	353,789	5,869	167.16	Reference (1.00)
		Statin user	100,658	1,436	144.23	0.63 (0.59–0.67)
Abnormal ALT	No	Non-user	186,499	2,046	110.65	Reference (1.00)
		Statin user	49,855	556	112.93	0.8 (0.73–0.88)
	Yes	Non-user	216,723	6,023	280.59	Reference (1.00)
		Statin user	63,498	1,285	204.45	0.59 (0.55–0.63)

All models were adjusted for adjusted for age, sex, residential area, household income, smoking, alcohol consumption, physical activity, hypertension, diabetes, liver cirrhosis, and abnormal alanine transaminase.

ALT, alanine aminotransferase; BMI, body mass index; HR, hazard ratio; LC, liver cirrhosis.

*Rates are expressed per 100,000 person-years.

previous study found that statins can disrupt the PI3K/Akt/mTOR signaling pathway by activating PTEN and dephosphorylating Akt and S6RP, both of which play key roles in cancer-related angiogenesis.[35] In parallel, LDL reduction also contributes to improved hepatic perfusion and reduced portal pressure,[36] as elevated LDL levels are known to impair endothelial function, increasing vascular resistance and promoting inflammation and fibrosis within the liver.[37,38] Above diverse mechanisms highlight the multifaceted role of statins in reducing LREs, emphasizing the interplay between their lipid-lowering and direct vascular effects.

In our analysis, stratification by ALT levels revealed a significant difference in the effect of statin on the risk of liver-related events between those with normal ALT (aHR 0.83, 95% CI 0.74–0.92) and abnormal ALT (aHR 0.60, 95% CI 0.56–0.65). Elevated ALT is a marker of liver damage and often indicates more advanced liver disease, which may explain the heightened benefit of statins in this population.[39] Despite concerns about statin-induced hepatotoxicity, a meta-analysis found no significant risk of liver function abnormalities in patients taking low-to-moderate doses of pravastatin, lovastatin, or simvastatin,[40] while pravastatin was specifically associated with improvements in transaminitis.[41] Overall, our results highlight the importance of considering baseline liver function in evaluating statin efficacy and suggest that statins could play a crucial role in preventing liver disease progression in patients with abnormal ALT levels.

Our study demonstrated a relatively low incidence rate of LREs, with an overall rate of 193.7 per 100,000 person-years. Stratified analysis revealed a significant disparity in LRE incidence: 150.1 per 100,000 person-years in the non-LC group *vs.* 6,460.3 per 100,000 person-years in the LC group. The overall low LRE rate is primarily attributable to the small proportion of patients with LC, as LC is a very well-known driver of LREs. However, as residual confounding might remain despite adjusting for key covariates, particularly because of the absence of noninvasive fibrosis tests (*e.g.* Fibrosis-4 or transient elastography), future studies incorporating these markers are needed. Such low rates of LREs in our study were in accordance with prior domestic study results (low rates of LC [2.22%] and HCC [0.77%] over 10 years),[42] but our overall LRE rates were still lower than those in Western populations.[43–45] This discrepancy may be attributed to differences in diagnostic methods, with Western studies often using more sensitive imaging techniques, leading to higher reported rates of disease progression. Furthermore, genetic predispositions, such as lower prevalence of patatin-like phospholipase domain-containing protein 3 and transmembrane 6 superfamily member 2 variants across different populations,[46] and lifestyle factors, including healthier diets and lower obesity rates,[47] might likely contribute to the slower disease progression in South Korean population. Further studies are also required considering population-specific factors.

Our study had several strengths. First, we utilized a representative cohort covering 97.2% of the general population in South Korea, allowing for a large sample size.[19] This could be one of the first studies to examine the effect of statins on liver-related prognosis using the new nomenclature of SLD, and it may also be the first such study conducted in Asian countries. We also considered socioeconomic status, lifestyle factors, and medical factors, as much as possible. Second, to ensure the robustness of our analyses, we used multiple statistical methods, including different landmark periods and time-dependent Cox models, to address immortal time bias and used PSM and IPTW to adjust for confounders. Moreover, constructing the cohort as a new user design minimizes the issues with left-truncated data. Finally, our stratified analysis highlights the efficacy of statins, particularly in patients with abnormal ALT levels.

However, this study has several limitations. First, owing to the limited information available in the NHIS database, unmeasured confounders such as liver function laboratory measurements, dietary habits, or genetic predispositions may not have been accounted for in our findings. Also, the use of ICD-10 codes to diagnose compensated LC may result in misclassification or under-reporting, as these codes may not fully capture cases without clear clinical symptoms. This could result in underestimating the overall prevalence of LC in our study. Second, we also acknowledge the limited utility of the FLI in identifying MetALD and the potential impact of alcohol consumption changes on gamma-glutamyltransferase as a component of the FLI. To address this concern, when we categorized participants into three subgroups according to dose of consistent alcohol consumption, MASLD, MetALD with low-dose alcohol, and MetALD with high-dose alcohol, the significant association between statin use and SLD regression in all subgroups was maintained. Further studies to develop additional simple biomarkers to identify MetALD may be necessary. Fourth, statin users tended to utilize healthcare services more frequently than non-users. Even though we demonstrated consistent results even after adjusting for this factor, the potential residual confounding associated with the likelihood of statin users engaging more frequently with healthcare services might not have been entirely addressed. Finally, there is the potential for misclassification of SLD, as our definition relies on biochemical scoring rather than imaging or pathological findings. To mitigate this limitation, we defined SLD based on two consecutive health checkup results, ensuring that the FLI cutoff was met on both occasions.

In summary, our study demonstrated a significant reduction in the risk of LREs among statin users with MASLD/MetALD. Therefore, statin therapy may be a viable preventive strategy to enhance liver-related outcomes in patients with MASLD/MetALD. Further well-designed studies are required to confirm these findings.

Affiliations

[1]*Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea;* [2]*Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea;* [3]*The Institute for Occupational Health, Yonsei University College of Medicine, Seoul, Republic of Korea;* [4]*Institute for Innovation in Digital Healthcare, Yonsei University Health System, Seoul, Republic of Korea;* [5]*Department of Public Health, Graduate School, Yonsei University, Seoul, Republic of Korea;* [6]*Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea;* [7]*Yonsei Liver Center, Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea*

Abbreviations

ACEi, angiotensin-converting enzyme inhibitors; aHR, adjusted hazard ratios; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; BB, non-selective and selective beta-blocker; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; DLC, decompensated liver cirrhosis; DPP4i, dipeptidyl peptidase-4 inhibitor; FLI, Fatty Liver Index; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; ICD-10, International Classification of Diseases 10th Revision; IPTW, inverse probability weighting; KLF2, Kruppel-like factor 2; LC, liver cirrhosis; LREs, liver-related events; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MET, metabolic equivalent of tasks; MetALD, MASLD with increased alcohol consumption; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NHIS, National Health Insurance Service; OLT, orthotopic liver transplantation; PSM, propensitiy score matching; ROC, receiver operating characteristic; SLD, steatotic liver disease; SMD, standardized mean difference; SU, metformin, sulfonylurea; TZD, thiazolidinedione.

Financial support

This work was in part supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2024-00455210).

Conflicts of interest

The authors have no conflicts of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: BY, BKK. Visualization: HP, JL. Investigation: BY, JL, BKK. Methodology: BY, J-HY. Data curation: BY, HP. Formal analysis: BY. Validation: J-HY.
Project administration: BKK. Software: J-HY. Resources: J-HY, BKK. Supervision: J-HY, BKK. Writing – original draft: BY, HP. Writing – review & editing: J-HY, BKK. Funding acquisition: BKK. Guarantors of the article: BKK, J-HY.

Data availability statement

Data and study materials are not available to other researchers because they originated from a nationwide database.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101313.

References

Author names in bold designate shared co-first authorship

[1] Chan WK, Chuah KH, Rajaram RB, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD): a state-of-the-art review. J Obes Metab Syndr 2023;32:197–213.
[2] **Kim GA**, **Moon JH**, Kim W. Critical appraisal of metabolic dysfunction-associated steatotic liver disease: implication of Janus-faced modernity. Clin Mol Hepatol 2023;29:831–843.
[3] Yoon EL, Jun DW. Waiting for the changes after the adoption of steatotic liver disease. Clin Mol Hepatol 2023;29:844–850.
[4] Miao L, Targher G, Byrne CD, et al. Current status and future trends of the global burden of MASLD. Trends Endocrinol Metab 2024;35:697–707.
[5] **Kim HK**, **Bae SJ**, Lee MJ, et al. Association of visceral fat obesity, sarcopenia, and myosteatosis with non-alcoholic fatty liver disease without obesity. Clin Mol Hepatol 2023;29:987–1001.
[6] Han SK, Baik SK, Kim MY. Non-alcoholic fatty liver disease: definition and subtypes. Clin Mol Hepatol 2023;29(Suppl.):S5–S16.
[7] **Nguyen VH**, **Le I**, Ha A, et al. Differences in liver and mortality outcomes of non-alcoholic fatty liver disease by race and ethnicity: a longitudinal real-world study. Clin Mol Hepatol 2023;29:1002–1012.
[8] Yun B, Park H, Ahn SH, et al. Liver cancer risk across metabolic dysfunction-associated steatotic liver disease and/or alcohol: a nationwide study. Am J Gastroenterol 2025;120:410–419.
[9] Kim DY. Changing etiology and epidemiology of hepatocellular carcinoma: asia and worldwide. J Liver Cancer 2024;24:62–70.
[10] **Moon JH**, **Jeong S**, Jang H, et al. Metabolic dysfunction-associated steatotic liver disease increases the risk of incident cardiovascular disease: a nationwide cohort study. EClinicalMedicine 2023;65:102292.
[11] **Park MJ**, **Kim H**, Kim MG, et al. Comparison of glucagon-like peptide-1 receptor agonists and thiazolidinediones on treating nonalcoholic fatty liver disease: a network meta-analysis. Clin Mol Hepatol 2023;29:693–704.
[12] Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med 2024;390:497–509.
[13] Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol 2019;74:1376–1414.
[14] **Ayada I**, **van Kleef LA**, Zhang H, et al. Dissecting the multifaceted impact of statin use on fatty liver disease: a multidimensional study. EBioMedicine 2023;87:104392.
[15] Zhou XD, Cai J, Targher G, et al. Metabolic dysfunction-associated fatty liver disease and implications for cardiovascular risk and disease prevention. Cardiovasc Diabetol 2022;21:270.
[16] **Zhou XD**, **Targher G**, **Byrne CD**, et al. An international multidisciplinary consensus statement on MAFLD and the risk of CVD. Hepatol Int 2023;17:773–791.
[17] Zou B, Odden MC, Nguyen MH. Statin use and reduced hepatocellular carcinoma risk in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2023;21:435. 44.e6.
[18] Zhou XD, Kim SU, Yip TC, et al. Long-term liver-related outcomes and liver stiffness progression of statin usage in steatotic liver disease. Gut 2024;73:1883–1892.
[19] **Song SO**, **Jung CH**, Song YD, et al. Background and data configuration process of a nationwide population-based study using the Korean national health insurance system. Diabetes Metab J 2014;38:395–403.
[20] Shin DW, Cho J, Park JH, et al. National general health screening program in Korea: history, current status, and future direction. Precision Future Med 2022;6:9–31.
[21] Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79:1542–1556.
[22] Nomura T, Ono M, Kobayashi K, et al. Validation of fatty liver index as a predictor of hepatic steatosis in Asian populations: impact of alcohol consumption and sex. Hepatol Res 2023;53:968–977.
[23] Takahashi S, Tanaka M, Higashiura Y, et al. Prediction and validation of nonalcoholic fatty liver disease by fatty liver index in a Japanese population. Endocr J 2022;69:463–471.
[24] Park JH, Hong JY, Han K, et al. Association between glycemic status and the risk of kidney cancer in men and women: a nationwide cohort study. Diabetes Care 2023;46:38–45.
[25] Jang H, Kim Y, Lee DH, et al. Outcomes of various classes of oral antidiabetic drugs on nonalcoholic fatty liver disease. JAMA Intern Med 2024;184:375–383.
[26] Yun B, Ahn SH, Yoon JH, et al. Statin use and risk of progression to liver cirrhosis in chronic hepatitis B independent of conventional risk factors: a nationwide study. Hepatol Commun 2022;6:2455–2464.
[27] Jeong SW, Kim SH, Kang SH, et al. Mortality reduction with physical activity in patients with and without cardiovascular disease. Eur Heart J 2019;40:3547–3555.
[28] Chun HS, Park S, Lee M, et al. Association of physical activity with the risk of hepatocellular carcinoma in patients with chronic hepatitis B. Cancers (Basel) 2021;13:3424.
[29] Sinn DH, Kang D, Guallar E, et al. Modest alcohol intake and mortality in individuals with elevated alanine aminotransferase levels: a nationwide cohort study. BMC Med 2022;20:18.
[30] Gracia-Sancho J, Russo L, García-Calderó H, et al. Endothelial expression of transcription factor Kruppel-like factor 2 and its vasoprotective target genes in the normal and cirrhotic rat liver. Gut 2011;60:517–524.
[31] Parmar KM, Nambudiri V, Dai G, et al. Statins exert endothelial atheroprotective effects via the KLF2 transcription factor. J Biol Chem 2005;280(29):26714–26719.
[32] **Marrone G**, **Russo L**, Rosado E, et al. The transcription factor KLF2 mediates hepatic endothelial protection and paracrine endothelial-stellate cell deactivation induced by statins. J Hepatol 2013;58:98–103.
[33] Trebicka J, Hennenberg M, Laleman W, et al. Atorvastatin lowers portal pressure in cirrhotic rats by inhibition of RhoA/Rho-kinase and activation of endothelial nitric oxide synthase. Hepatology 2007;46:242–253.
[34] Likus W, Siemianowicz K, Bieńk K, et al. Could drugs inhibiting the mevalonate pathway also target cancer stem cells? Drug Resist Updat 2016;25:13–25.
[35] Wang T, Seah S, Loh X, et al. Simvastatin-induced breast cancer cell death and deactivation of PI3K/Akt and MAPK/ERK signalling are reversed by metabolic products of the mevalonate pathway. Oncotarget 2016;7:2532–2544.

[36] Abraldes JG, Rodríguez-Vilarrupla A, Graupera M, et al. Simvastatin treatment improves liver sinusoidal endothelial dysfunction in CCl4 cirrhotic rats. J Hepatol 2007;46:1040–1046.
[37] Catapano AL, Pirillo A, Norata GD. Vascular inflammation and low-density lipoproteins: is cholesterol the link? A lesson from the clinical trials. Br J Pharmacol 2017;174:3973–3985.
[38] Vairappan B. Endothelial dysfunction in cirrhosis: role of inflammation and oxidative stress. World J Hepatol 2015;7:443–459.
[39] Thakur S, Kumar V, Das R, et al. Biomarkers of hepatic toxicity: an overview. Curr Ther Res Clin Exp 2024;100:100737.
[40] de Denus S, Spinler SA, Miller K, et al. Statins and liver toxicity: a meta-analysis. Pharmacotherapy 2004;24:584–591.
[41] Calderon RM, Cubeddu LX, Goldberg RB, et al. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. Mayo Clin Proc 2010;85:349–356.
[42] **Park JW**, **Yoo JJ**, Lee DH, et al. Evolving epidemiology of non-alcoholic fatty liver disease in South Korea: incidence, prevalence, progression, and healthcare implications from 2010 to 2022. Korean J Intern Med 2024;39:931–944.
[43] Loomba R, Wong R, Fraysse J, et al. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. Aliment Pharmacol Ther 2020;51:1149–1159.
[44] Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113–121.
[45] Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2021;18:223–238.
[46] Kozlitina J, Sookoian S. Global epidemiological impact of PNPLA3 I148M on liver disease. Liver Int 2025;45:e16123.
[47] **Quek J**, **Chan KE**, **Wong ZY**, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2023;8:20–30.

Keywords: Metabolic dysfunction-associated steatotic liver disease; Statin; Liver-related events; Effect.
Received 16 October 2024; received in revised form 17 December 2024; accepted 19 December 2024; Available online 24 December 2024