Statin Use and Risk of Hepatocellular Carcinoma and Liver Fibrosis in Chronic Liver Disease

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Introduction

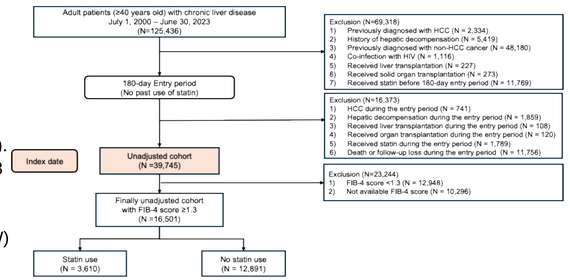
- The burden of hepatocellular carcinoma (HCC) is increasing worldwide, with metabolic and alcohol-related liver diseases now emerging as leading causes.
- Statins may protect against HCC by reducing liver inflammation and fibrosis, but evidence remains limited regarding their impact on fibrosis progression over time.

Aim

- To investigate the association between statin use and risk of incident HCC and hepatic decompensation and analyze changes in liver fibrosis among patients with significant fibrosis, leveraging data from a large-scale hospital registry database.

Methods

- **Design**: Historical cohort study using the RPDR database (Mass General Brigham, Boston), covering ~4 million patients.
- **Population**: Adults ≥40 years with chronic liver disease (CLD) from 2000–2023; final sample included 16,501 patients with baseline FIB-4 ≥1.3.
- **Exposure**: Statin use defined as ≥30 cumulative defined daily doses (cDDD); categorized into <30, 30–599, and ≥600 cDDD.
- **Outcomes**: ***Primary—incident hepatocellular carcinoma (HCC);*** Secondary—hepatic decompensation (e.g., variceal bleeding, ascites).
- **Fibrosis Assessment**: Serial FIB-4 score changes assessed in 7,038 patients at 3-year follow-up; transitions across fibrosis risk groups compared.
- **Statistical Methods**: Inverse probability of treatment weighting (IPTW) and Cox regression models with competing risk adjustment.
- **Sensitivity Analyses**: Included analyses without IPTW, excluding competing risks, PS-matched analyses, and negative control outcomes.



Results

Table 1. Characteristics of the Pooled Study Population of 16,501 Patients, According to Statin-Use Status

Characteristics	Patients, No. (%)			
	No Statin Use (N=12,891)	Statin Use (N=3,610)	SMD before IPTW	SMD after IPTW
Demographics				
Age, mean (SD), y	58.5 (11.0)	63.7 (10.1)	0.49	0.082
Sex, female	5,335 (41.4)	1,415 (39.2)	0.02	0.075
Race and ethnicity				
Asian / African American	472 (3.7)/784 (6.1)	174 (4.8) / 283 (7.8)	0.01/0.02	0.001/-0.001
Caucasian / Other	10,235 (79.3)/1,400 (10.9)	2,788 (77.3) / 365 (10.1)	-0.02/-0.01	-0.001/0.001
Body mass index				
<25 kg/m²	1,570 (12.2)	477 (13.2)	0.01	0.006
≥25 kg/m² and <30 kg/m²	2,080 (16.1)	938 (26.0)	0.10	0.008
≥30 kg/m²	2,770 (21.5)	1,425 (39.5)	0.18	0.016
Not available	6,471 (50.2)	770 (21.3)	-0.29	-0.030
Comorbidities[b]				
Etiology of chronic liver disease				
Hepatitis B virus infection	562 (4.4)	209 (5.8)	0.01	-0.013
Hepatitis C virus infection	2,422 (18.8)	756 (20.9)	0.02	-0.043
Autoimmune hepatitis	301 (2.3)	43 (1.2)	-0.01	0.002
Primary biliary cholangitis	419 (3.3)	147 (4.1)	0.01	-0.003
Alcoholic hepatitis	2,681 (20.7)	500 (13.9)	-0.07	-0.012
MASLD	4,004 (31.1)	1,100 (30.5)	-0.01	0.054
Cryptogenic cirrhosis	1,337 (10.4)	205 (5.7)	-0.05	0.014
Others	1,165 (9.0)	650 (17.9)	0.09	0.001
Cirrhosis	5,476 (42.5)	1,258 (34.8)	-0.08	-0.046
Diabetes	2,185 (16.9)	1,532 (42.4)	0.25	0.045
Hypertension	5,599 (43.4)	2,868 (79.4)	0.36	0.038
Coronary artery disease	1,875 (14.5)	1,462 (40.5)	0.26	0.028
Dyslipidemia	3,122 (24.2)	2,624 (72.7)	0.48	0.035
Chronic kidney disease	729 (5.7)	459 (12.7)	0.07	0.028
Median FIB4 score[d]	2.3 (1.6–4.2)	1.9 (1.5–2.8)	-0.20	-0.030
FIB-4 score grade				
Intermediate (1.3 ≤FIB-4≤2.67)	6,598 (51.2)	2,368 (65.6)	0.14	-0.016
High (FIB-4 >2.67)	5,421 (42.1)	983 (27.2)	-0.15	-0.002
Medications				
Metformin use	810 (6.3)	861 (23.9)	0.18	0.020
Aspirin use	2,593 (20.1)	2,045 (56.6)	0.37	0.056
Fibrate use	188 (1.5)	170 (4.7)	0.03	0.008
Nicotinic acid use	57 (0.4)	55 (1.5)	0.01	0.001
Bile acid sequestrants use	172 (1.3)	66 (1.8)	0.01	0.001
SGLT-2 inhibitor use	49 (0.4)	46 (1.3)	0.01	0.001
Interferon use	58 (0.4)	88 (2.4)	0.02	0.003
Oral antiviral therapy				
Anti-HBV	145/562 (25.8)	74/209 (35.4)	0.01	-0.002
Anti-HCV	143/2,422 (5.9)	190/756 (25.1)	0.04	0.004
Laboratory parameters, median (IQR)				
Platelet count – 1,000/mm³	181 (128–228)	197 (158–237)	0.21	0.040
AST, U/mL	42 (28–74)	32 (23–49)	-0.12	-0.019
ALT, U/mL	35 (21–64)	29 (19–48)	-0.11	0.06
Albumin, g/L[c]	4.0 (3.5–4.4)	4.2 (3.8–4.5)	0.32	-0.072
Total bilirubin, mg/dL[c]	0.8 (0.4–1.1)	0.5 (0.4–0.8)	-0.25	-0.016
Imaging test				
Number of abdomen image				
<1 exam per year	3,764 (29.2)	1,298 (36.0)	0.07	0.015
1–2 exams per year	1,463 (11.3)	446 (12.4)	0.01	-0.010
>2 exams per year	2,669 (20.7)	629 (17.4)	-0.03	0.036
Not identified	4,995 (38.7)	1,237 (34.3)	-0.04	-0.011

Figure 1. Cumulative Incidence of Hepatocellular Carcinoma and Hepatic Decompensation among Statin Users and Nonusers

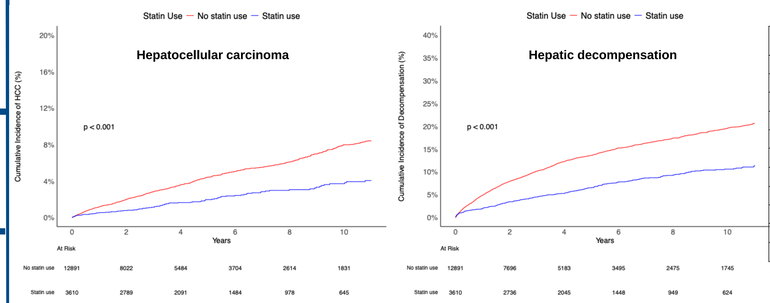


Table 2. Association of Statin Use on Risk of Incident Hepatocellular Carcinoma

	No. with Event /Total No.	10-Yr Cumulative Incidence	ARD (95% CI)	Hazard Ratio (95% CI)	
				Unadjusted	Adjusted[a]
Primary outcome (HCC)					
No statin use	653/12,891	8.0%	–	1 (reference)	1 (reference)
Statin use	102/3,610	3.8%	-4.2 (-5.3 to -3.1)	0.52 (0.47 to 0.59)	0.67 (0.59 to 0.76)
Incident HCC according to statin type					
No statin use	653/12,891	8.0%	–	1 (reference)	1 (reference)
Hydrophilic statin	18/680	4.1%	-3.9 (-6.2 to -1.6)	0.75 (0.60 to 0.93)	0.79 (0.63 to 0.99)
Lipophilic statin	84/2,930	3.7%	-4.3 (-5.5 to -3.1)	0.48 (0.42 to 0.55)	0.64 (0.55 to 0.73)
Incident HCC according to statin use duration					
No statin use	653/12,891	8.0%	–	1 (reference)	1 (reference)
30-599 cDDD	27/1,518	3.8%	-4.2 (-6.2 to -2.2)	0.69 (0.58 to 0.81)	0.79 (0.67 to 0.93)
≥600 cDDD	75/2,092	3.5%	-4.5 (-5.6 to -3.2)	0.45 (0.39 to 0.52)	0.60 (0.52 to 0.70)

ARD: absolute risk difference, CI: confidence interval, cDDD: cumulative daily defined dose

Figure 2. Cumulative Incidence of Hepatocellular Carcinoma and Hepatic Decompensation by Statin Type and Duration

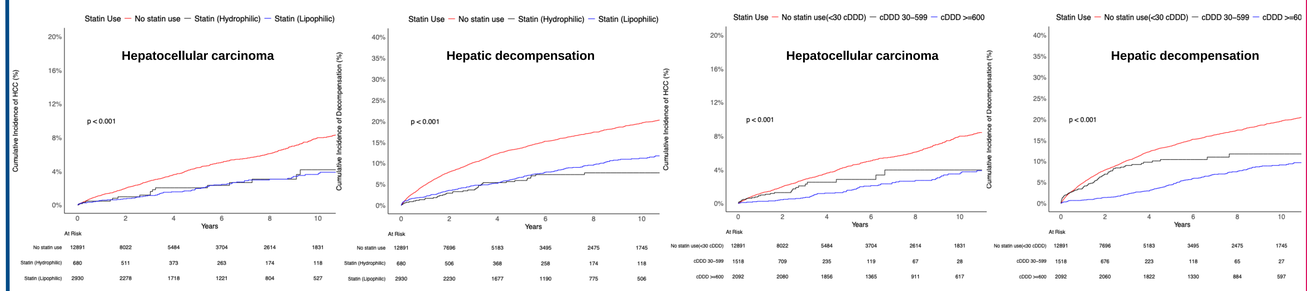
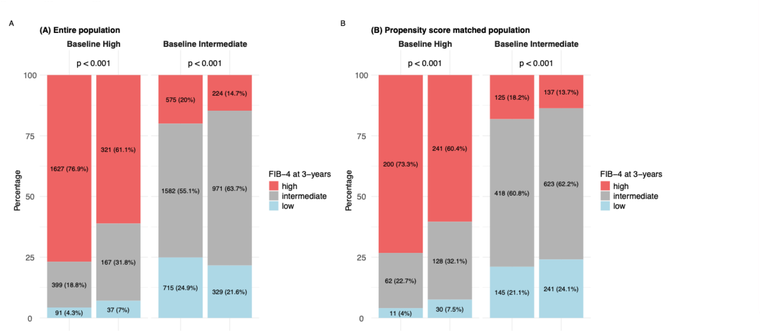


Figure 3. FIB4- group Transitions at 3 Years by Statin Use Among Patients with Baseline High and Intermediate FIB-4 Scores



Conclusions

- Statin use was associated with a reduced risk of hepatocellular carcinoma (HCC) and slower progression of liver fibrosis in patients with chronic liver disease (CLD).
- These associations were especially prominent with **lipophilic statins** and **longer duration of statin therapy** (≥600 cDDD).
- Among patients with **intermediate-to-high baseline FIB-4 scores**, statin users showed **more stable fibrosis trajectories** and **lower transition rates to higher fibrosis risk**.
- Statin users with **high baseline FIB-4 scores** were more likely to improve or remain stable, compared to nonusers.
- These findings support the **potential chemopreventive role of statins** in reducing HCC risk by mitigating liver fibrosis progression in at-risk CLD populations.

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