**Title:** **Long-term Liver-related Outcomes and Liver Stiffness Progression of Statin Usage in** **Steatotic Liver Disease.**

**Running Title:** Statin Use for MASLD

**Authors’ names:**

Xiao-Dong Zhou1, Seung Up Kim2, Terry Cheuk-Fung Yip3,4, Salvatore Petta5, Atsushi Nakajima6, Emmanuel Tsochatzis7, Jérôme Boursier8, Elisabetta Bugianesi9, Hannes Hagström10,11, Wah-Kheong Chan12, Manuel Romero-Gomez13, José Luis Calleja14, Victor de Lédinghen15, Laurent Castéra16, Arun J. Sanyal17, Boon-Bee George Goh18, Philip Noel Newsome19, Jian-Gao Fan20, Michelle Lai21, Céline Fournier15, Hye Won Lee2, Grace Lai-Hung Wong3,4, Angelo Armandi9, Ying Shang10, Grazia Pennisi5, Elba Llop14, Masato Yoneda6, Marc de Saint-Loup8, Clemence M Canivet8,Carmen Lara-Romero13, Rocio Gallego-Durán13, Amon Asgharpour17, Kevin Kim-Jun Teh18, Sara Mahgoub19, Mandy Sau-Wai Chan15, Huapeng Lin23,24,25, Wen-Yue Liu26, Giovanni Targher27,28, Christopher D. Byrne29, Vincent Wai-Sun Wong3,4\*,Ming-Hua Zheng30,31,32\*

**Institutions:**

1Department of Cardiovascular Medicine, the Heart Center, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China;

2Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea;

3Medical Data Analytics Centre, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China;

4State Key Laboratory of Digestive Disease, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China;

5Sezione di Gastroenterologia, Di.Bi.M.I.S., University of Palermo, Italy;

6Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan;

7University College London Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom;

8Hepato-Gastroenterology and Digestive Oncology Department, Angers University Hospital, Angers, France;

9Department of Medical Sciences, Division of Gastroenterology and Hepatology, A.O. Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy;

10Department of Medicine, Huddinge, Karolinska Institutet, Sweden;

11Division of Hepatology, Department of Upper GI Diseases, Karolinska University Hospital, Stockholm, Sweden;

12Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, University of Malaya, Malaysia;

13Digestive Diseases Unit and CIBERehd, Virgen Del Rocío University Hospital, Seville, Spain;

14Department of Gastroenterology and Hepatology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain;

15Echosens, Paris, France;

16Université Paris Cité, UMR1149 (CRI), INSERM, Paris, France; Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris (AP-HP), Clichy, France;

17Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA, USA;

18Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore;

19Institute of Hepatology, Faculty of Life Sciences & Medicine, King’s College London and King’s College Hospital, London, UK;

20Department of Gastroenterology and Hepatology, School of Medicine, Shanghai Jiao Tong University, Shanghai, China;

21Division of Gastroenterology & Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA;

22Centre d’ Investigation de la Fibrose Hépatique, Haut-Lévêque Hospital, University Hospital of Bordeaux, Pessac, France;

23Department of Gastroenterology and Hepatology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;

24Center for Digestive Diseases Research and Clinical Translation of Shanghai Jiao Tong University, Shanghai, China;

25Shanghai Key Laboratory of Gut Microecology and Associated Major Diseases Research, Shanghai, China;

26Department of Endocrinology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, 325000, China;

27Department of Medicine, University of Verona, Verona, Italy;

28Metabolic Diseases Research Unit, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar di Valpolicella, Italy;

29Southampton National Institute for Health and Care Research Biomedical Research Centre, University Hospital Southampton, and University of Southampton, Southampton General Hospital, Southampton, UK;

30MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

31Institute of Hepatology, Wenzhou Medical University, Wenzhou, China;

32Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China.

**\*Corresponding author:** Vincent Wai-Sun Wong and Ming-Hua Zheng

Prof Vincent Wong, MD, PhD

Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong, China

Email: wongv@cuhk.edu.hk; phone: 852-35054205

Ming-Hua Zheng, MD, PhD

MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China.

Email: zhengmh@wmu.edu.cn; phone: (86) 577-55579611; fax: (86) 577-55578522

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**Abstract**

**Background:** Statins have multiple benefits in patients with metabolic-associated steatotic liver disease (MASLD).

**Aim:** To explore the effects of statins on the long-term risk of all-cause mortality, liver-related clinical events (LRE) and liver stiffness progression in patients with MASLD.

**Methods:** This cohort study collected data on patients with MASLD undergoing at least two vibration-controlled transient elastography examinations at 16 tertiary referral centers. Cox regression analysis was performed to examine the association between statin usage and long-term risk of all-cause mortality and LREs stratified by compensated advanced chronic liver disease (cACLD): baseline liver stiffness measurement (LSM) of ≥10 kPa. Liver stiffness progression was defined as LSM increase of ≥20% for cACLD and from <10 kPa to ≥10 or LSM for non-cACLD. Liver stiffness regression was defined as LSM reduction from ≥10 kPa to <10 or LSM decrease of ≥20% for cACLD.

**Results:** We followed-up 7,988 patients with baseline LSM 5.9 kPa (IQR 4.6-8.2) for a median of 4.6 years. At baseline, 40.5% of patients used statins, and cACLD was present in 17%. Statin usage was significantly associated with a lower risk of all-cause mortality (adjusted HR=0.233; 95%CI 0.127-0.426) and LREs (adjusted HR=0.380; 95%CI 0.268-0.539). Statin usage was also associated with lower liver stiffness progression rates in cACLD (HR=0.542; 95%CI 0.389-0.755) and non-cACLD (adjusted HR=0.450; 95%CI 0.342-0.592), but not with liver stiffness regression (adjusted HR=0.914; 95%CI 0.778-1.074).

**Conclusions:** Statin usage was associated with a relatively lower long-term risk of all-cause mortality, LREs, and liver stiffness progression in patients with MASLD.

**Keywords:** metabolic dysfunction-associated fatty liver disease, metabolic dysfunction-associated steatotic liver disease, vibration-controlled transient elastography, liver fibrosis, prognosis.

**Introduction**

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a significant health concern affecting up to 30% of people worldwide, which is mainly caused by the increasing global prevalence of obesity and metabolic disorders.1,2 Despite major efforts to develop effective treatments, there has only been one drug (resmetirom) recently receiving conditional approval by the US Food and Drug Administration for treating patients with metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced hepatic fibrosis.3,4

Statins are widely recognized for their effectiveness in reducing the risk of cardiovascular disease (CVD) by lowering plasma low-density lipoprotein (LDL)-cholesterol concentrations by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase.5,6 Most patients with MASLD have indications for statins, including dyslipidemia, pre-existing CVD or high risk of CVD.7 Statins exert anti-inflammatory, antifibrotic, antithrombogenic, and antioxidant effects, which may also aid in reducing the progression of liver fibrosis in MASLD.8-10 This has generated increasing interest in the potential of statins to manage complications in people with MASLD, in which CVD represents the leading cause of death.10-12 However, statins are still not widely used in patients with chronic liver disease, mainly due to concerns about possible statin-induced liver damage and muscle weakness.13 Several studies have shed light on the efficacy of statin usage in patients with MASLD, without and with cirrhosis, and have also shown encouraging results in recent years.14 Consequently, recent expert recommendations have strongly recommended the use of statin therapy for treating patients with MASLD who have pre-existing CVD or are at high risk of CVD.15

Statins have not been shown to improve MASH or liver fibrosis in histological studies. However, numerous observational studies have reported an association between statin use and a lower incidence of hepatocellular carcinoma (HCC).16 If this protective effect is real, it is unclear whether it is mediated by preventing liver fibrosis progression.

Therefore, this observational multicenter cohort study aimed to explore the effects of statins on the long-term risk of all-cause mortality, liver-related clinical outcomes and liver stiffness progression in patients with MASLD.

**Methods**

***Study Design and Participants***

This cohort study (the VCTE-Prognosis study) was conducted on patients with MASLD who underwent vibration-controlled transient elastography (VCTE) examinations at 16 centers in the United States, Europe, and Asia. Detailed information on the VCTE-Prognosis study has been presented in a previously published work.17 This study retrospectively analyzed patient encounters recorded in the electronic medical records. Patients aged ≥18 years with MASLD diagnosed by liver histology (steatosis in ≥ 5% of hepatocytes) or imaging methods (ultrasonography, computed tomography, magnetic resonance imaging, or controlled attenuation parameter ≥ 248 dB/m by VCTE) were eligible.18,19 Patients with other liver diseases, such as chronic viral hepatitis, HIV infection, excessive alcohol consumption (>30 g/day in men and >20 g/day in women), drug-induced hepatic steatosis (e.g., usage of systemic steroids), or a history of HCC, hepatic decompensation, liver resection, liver transplant, or other malignancies were excluded (**Figure 1**).

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. The protocol of this study underwent approval by the Institutional Review Boards of all participating centers. Adherence to the Declaration of Helsinki principles was undertaken and the need for informed written consent was waived due to its retrospective nature.

***Clinical, biochemical and VCTE assessments***

During each visit to the clinic, the patient's medical history was recorded, and body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters. After at least 8 hours of fasting, a venous blood sample was taken to examine kidney and liver biochemistry and complete blood count. Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were performed on FibroScan devices (Echosens, Paris, France) by healthcare professionals who were trained as per the manufacturer's instructions. LSMs were considered valid and reliable if ten measurements were obtained with interquartile ranges (IQRs)/medians of less than 30%. While using the probe (M or XL), the instructions given by the manufacturer were followed. The XL probe was only available from 2014 for study sites. To ensure accuracy, patients enrolled in the study were required to have at least 10 valid acquisitions. Compensated advanced chronic liver disease (cACLD) was defined as baseline LSM of ≥10 kPa.

***Study outcomes***

As no patient had a history of decompensating events, we classified cACLD based on Baveno VII criteria and divided patients into “cACLD” (LSM ≥ 10 kPa) and “No cACLD” (LSM < 10 kPa) at baseline.20 The diagnosis of the events was based on prospective follow-up, medical record review, or validated registries with positive predictive values of at least 90%. The primary study outcome was a composite outcome inclusive of all-cause death and liver-related events (LREs), including the development of cirrhosis (cirrhosis, decompensation, or portal hypertension ICD codes), HCC or liver-related mortality (including liver transplantation). The secondary study outcome was the change in hepatic steatosis and liver stiffness (assessed by VCTE). For MASLD patients with cACLD at baseline (i.e., those with baseline LSM ≥ 10 kPa), a clinically relevant increase in LSM was defined as at least a 20% increase in LSM (i.e., liver stiffness progression).21 A clinically relevant decrease in LSM was defined as a follow-up LSM of less than 10 kPa or baseline LSM of less than 20 kPa with a decrease of at least 20% (liver stiffness regression).21 For MASLD patients without cACLD at baseline (i.e., those with baseline LSM < 10 kPa), a clinically relevant LSM increased if the follow-up LSM was ≥ 10 kPa (liver stiffness progression).21 The remaining patients were considered to be “liver stiffness stable”. 21 For patients with multiple VCTE examinations, we selected the first and last examinations if they did not experience the event of interest, such as the VCTE for liver stiffness progression/regression. If the event of interest occurred, we included the first event and the first related VCTE examination.

***Statin exposure***

All patients who were prescribed statin medications during the study observation period were identified. The clinical follow-up period was between the first VCTE and the final clinical follow-up or death or LRE, whichever came first. Statin prescriptions included simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, and pitavastatin. The cumulative defined daily dose (cDDD) is the total sum of all defined daily doses of a specific drug used during the follow-up period. The usage of statins was defined as the consistent use of statins on most days for more than one month within a year, with an average dose of at least 30 cDDDs per year, consistent with prior studies.22-24

***Statistical Analysis***

All statistical analyses were performed using the IBM SPSS software, version 23.0 for Windows. Continuous variables were expressed as means ± SD or medians (interquartile ranges, IQR), and categorical variables as percentages. Statistical comparisons between the study groups were carried out using the unpaired Student’s *t*-test (for normally distributed continuous variables), the Mann-Whitney U test (for non-normally distributed continuous variables), and the chi-squared test (for categorical variables). During the follow-up, we performed unadjusted and adjusted Cox proportional hazards models to examine the association between statin usage and the risk of long-term clinical outcomes (all-cause death and LREs) and LSM changes, using hazard ratios (HR) and 95% confidence intervals (CI). We conducted a graphical assessment and confirmed that the proportional hazards assumption was satisfied by plotting Schoenfeld residuals against ranks of time, and no violation was found. Adjustments were undertaken for clinically important covariates, including age, sex, BMI (continuous), diabetes, hypertension, baseline LSM, and CAP. Kaplan-Meier survival analysis was performed, and the log-rank test was used to determine any significant differences between the curves. A p-value <0.05 was considered statistically significant.

We conducted multiple sensitivity analyses to assess the reliability of our findings. First, to minimize the effect of immortal time bias (people with more prolonged survival might have a greater possibility for events), we left-truncated the follow-up period at three years and conducted time-to-event analyses again. Second, to test if the LSM cutoff used to define liver stiffness regression and progression may impact the results, we have also provided HRs for the primary outcome by increasing the LSM cutoff to 30%. This was done to alleviate any concerns regarding the presence of enough signal to ensure that a genuine LSM change is being measured. Third, we also conducted competing risk regression analysis using the Fine and Gray's model to estimate subdistribution hazard ratios (SHR) for non-outcome death. Fourth, we conducted an analysis using propensity score matching (PSM) to confirm our findings. We performed PSM to balance the baseline characteristics between patients with and without statins. We used one-to-one propensity score matching to select similar groups of individuals prescribed statins and those not, based on age, sex, BMI, hypertension, diabetes, LSM, and CAP at baseline. The adjustment was made following the calibration of the caliper width to 0.1 of the standard deviation found in the logit-transformed propensity scores. The balance of potentially associated factors between the two-propensity score-matched groups was evaluated using standardized mean differences. Adjusted Cox proportional hazards models were also applied, with robust standard errors accounting for the clustering of matched pairs.

**Results**

***Participants Characteristics***

Between February 2004 and January 2023, we found 17,949 patients who underwent one or more VCTE examinations. After screening for inclusion and exclusion criteria, we excluded 9961 patients, leaving 7988 patients with MASLD in the final analysis, as shown in **Figure 1**. Compared to non-statin users, patients with statin usage were older (56.3 ± 12.0 vs. 50.5 ± 14.3 years, P < 0.001) and more likely to have hypertension (48.8% vs. 29.0%, P < 0.001) and type 2 diabetes mellitus (51.2% vs. 24.1%, P < 0.001). Despite being older, patients taking statins had a lower prevalence of cACLD (11.8% vs. 20.9%, P < 0.001), whereas no significant differences were found in the prevalence of liver steatosis (CAP: 299 (IQR: 273 - 330) dB/m vs. 303 (IQR 273 - 335) dB/m, P = 0.062). Detailed clinical features of the population, stratified by statin usage, are shown in **Table 1.**

***Association of Statin Usage and Long-Term Adverse Clinical Outcomes***

During a median follow-up of 4.6 years (IQR: 3.0 - 6.4 years), 87 deaths and 208 LREs occurred in the whole cohort of participants (**Table 2**). In particular, 68 deaths and 156 LREs occurred in non-statin users with an incidence rate of 2.9 and 6.7 per 1000 person-years, while 19 deaths and 52 LREs occurred in statin users with an incidence event rate of 1.1 and 3.0 per 1000 person-years, respectively (**Table 3**). Compared to non-statin users, patients treated with statins had a significantly lower incidence of all-cause death and LREs (both P < 0.001). After adjusting for potential confounding factors, the Cox regression models indicated that statin usage was significantly associated with a lower risk of all-cause mortality (HR = 0.233; 95% CI 0.127 - 0.426, P < 0.001) and LREs (HR = 0.380; 95% CI 0.268 - 0.539, P < 0.001). Subgroup analysis also demonstrated that this association persisted in both non-cACLD and cACLD groups (all P < 0.001). The Kaplan-Meier survival analysis showed a sustained decrease in the cumulative incidence rates of all-cause mortality and LRE in statin users compared to non-users **(Figure 2**).

***Association between Statin Usage and LSM Changes***

Patients with liver stiffness progression were more likely to develop clinical outcomes, including all-cause mortality and LRE, compared to those with stable liver stiffness, in both cACLD and non-cACLD groups (**Supplementary Figure 1 & Supplementary Table 1**). In the non-cACLD group, we found a ~3.8-fold risk of all-cause mortality (HR = 3.797; 95% CI 1.522 - 9.474, P < 0.001) and a ~7.5-fold risk of developing incident LREs (HR = 7.548; 95% CI 3.844 - 14.823, P < 0.001) in patients with liver stiffness progression compared to those with stable liver stiffness. In the cACLD group, the adjusted HRs were 5.576 with a 95% CI of 2.598 to 11.968 (P < 0.001) for all-cause death and 21.338 with a 95% CI of 13.061 to 34.858 (P < 0.001) for incident LREs in patients with liver stiffness progression compared to those with stable liver stiffness.

We also assessed the association between statin usage and changes in LSMs (**Figure 3 & Supplementary Table 2**). During a median VCTE follow-up of 3.0 (IQR: 1.9 - 4.5) years, compared to non-statin users, statin users had a 55% lower risk of liver stiffness progression in the non-cACLD group and a 46% lower risk of liver stiffness progression in the cACLD group (both P < 0.001) (**Table 4**). Conversely, the association between statin usage and liver stiffness regression was not statistically significant (HR = 0.914; 95% CI 0.778 - 1.074, P = 0.275). In the Kaplan-Meier survival analysis, we found that statin users had a significantly lower incidence of liver stiffness progression than non-statin users in both cACLD and non-cACLD groups (**Figure 4**).

**Sensitivity Analyses**

Our results remained robust and consistent in all sensitivity analyses (**Supplementary Table 3**). We also categorized statin users into those using lipophilic or hydrophilic statins and found that the results remained unchanged (**Supplementary Figure 2 & Supplementary Figure 3**). In an analysis where we considered only individuals who had been event-free for at least 3 years after their initial VCTE, we found that statin usage was significantly associated with a lower risk of all-cause death and LREs, with an HR of 0.277 (95%CI 0.145 - 0.529) and 0.411 (95%CI 0.283 - 0.596). For liver stiffness changes, statin usage remained an independent predictor of liver stiffness progression in the whole cohort (HR = 0.389, 95% CI 0.308 - 0.491, P < 0.001). In a competing risk regression analysis with all-cause deaths as the competing risk, the HRs showed similar results for LREs (SHR = 0.441 95% CI 0.321 - 0.604, P < 0.001) and liver stiffness progression (SHR = 0.501, 95% CI 0.410 - 0.611). When setting the LSM-change cutoff from 20% to 30%, statin usage was found to lower the risk of liver stiffness progression compared to those who did not assume statins (HR = 0.414; 95% CI 0.332 – 0.515, P < 0001). Following a PSM analysis, we balanced baseline clinical and biochemical characteristics between patients with statin usage and those without. Each group, consisting of 2,499 patients, was paired based on the congruence of their demographic and clinical profiles, as detailed in **Supplementary Table 4**. This PSM process ensured that the standardized mean differences for most underlying factors remained below the threshold of 0.1. The results of PMS analysis were consistent and confirmed a substantially lower risk of all-cause death, LREs and liver stiffness progression rates for statin usage even after adjusting for potential confounders (all-cause death: HR = 0.273 95% CI 0.131 - 0.566, P < 0.001; LREs: HR = 0.524, 95% CI 0.343 - 0.802, P = 0.003; liver stiffness progression: HR = 0.449, 95% CI 0.354 - 0.570, P < 0.001).

**Discussion**

In this large multicenter VCTE-prognosis study, compared with non-statin usage, statin usage was associated with a substantially lower long-term risk of all-cause mortality, LREs and liver stiffness progression in individuals with MASLD.

***Effect of statin usage on*** ***all-cause death and LREs***

An important finding of our cohort study is that statin usage was associated with a marked reduction in the risk of all-cause death and LREs over a median follow-up of 4.6 years. Limited by the short follow-up period and low incidence of liver clinical outcomes, there have been few studies investigating the relationship between statin usage and the risk of adverse clinical outcomes, such as all-cause death and LREs, especially in MASLD patients without cACLD.16,25,26 A longitudinal retrospective analysis of 12,538 patients with MASLD using the National Health and Nutritional Examination Survey (NHANES) 1999-2018 database found that statin usage was significantly associated with a lower risk of all-cause and cancer-related mortality.25 A post-hoc analysis of three large randomized controlled trials (RCTs) involving over 11,000 patients with MASLD showed that atorvastatin usage significantly reduced serum liver enzyme levels and improved liver fat content.8 Compared to MASLD/ MASH patients who did not receive statins, those taking statins had a 50% reduction in CVD morbidity and mortality.8 Phase 3 RCTs are ongoing to evaluate the effect of statins on the long-term risk of LREs in patients with MASLD or MASH.27-29 This patient population is at high risk of developing fatal and nonfatal CVD events, and the use of statins may offer a substantial reduction in adverse cardiovascular and liver-related outcomes, which could also be of potential benefit for reducing the progression of liver disease over time. Previous studies have reported some protective effects of statin usage on chemoprevention and treatment of various cancer types, including HCC prevention in patients with MASLD.26 A recent meta-analysis including 242,751 patients showed that statin use was associated with a lower risk of HCC overall (HR: 0.52; 95% CI: 0.37–0.72) and in subgroup analyses for MASLD (HR: 0.68; 95% CI: 0.59–0.77; p < 0.01).16

***Effect of statin usage*** ***on liver stiffness progression***

Another important finding of our cohort study is that statin usage was significantly associated with a lower risk of liver stiffness progression in both cACLD and non-cACLD patients but did not reach statistical significance for liver stiffness regression. To our knowledge, this is the largest observational cohort study involving approximately 8,000 individuals exposed to statins, with serial VCTE results for each individual, which allowed for a more accurate diagnosis and dynamic staging of liver fibrosis. Currently, there are few studies on the long-term effects of statins on liver stiffness progression in MASLD.30 Using liver histopathology data from a nationwide Swedish cohort of 3,862 noncirrhotic individuals with various chronic liver diseases and statin exposure, Sharma et al. reported that statin usage was associated with lower rates of progression to cirrhosis (HR 0.62; 95% CI 0.49-0.78), HCC (HR 0.44; 95% CI 0.27-0.71), and liver-related mortality (HR 0.55; 95% CI 0.36-0.82).23 In a cross-sectional analysis of the NHANES 2017-18 database involving 744 patients with type 2 diabetes and VCTE results, Ciardullo et al. found that statin use was associated with lower odds of advanced liver fibrosis (OR 0.35; 95% CI 0.13 - 0.90), but no significant interaction was found between statin usage and hepatic steatosis (as assessed with CAP).30 In another recent cross-sectional study of 346 patients with biopsy-proven MASLD and type 2 diabetes, Nascimbeni et al. showed that statin use was negatively associated with significant liver fibrosis (≥ F2).31 A large population-based study was conducted on 712,262 subjects with MASLD (defined as FLI > 60) using data from the National Health Information Database of the Republic of Korea, collected in 2010 and followed-up until 2016.32 Of these, 111,257 subjects had a BARD score ≥ 2 and were categorized as liver fibrosis cases. The results of this cross-sectional study showed that statin usage was associated with a lower likelihood of significant liver fibrosis (adjusted OR 0.43; 95% CI 0.42–0.44), independent of diabetes status. In a European study of 1,201 patients with biopsy-proven NASH (107 took statins for at least six months), the authors reported that individuals on statin treatment had significantly lower odds for hepatic steatosis, NASH and advanced fibrosis than those who were not on statins.33 It is plausible that the potential benefits of statin usage, such as its anti-inflammatory, vascular, and tissue healing properties, could help prevent liver fibrosis progression. However, while no long-term phase 3 RCTs have been undertaken on the effect of statins on liver fibrosis in humans, available evidence suggests that statins generally have a beneficial effect on the severity of MASLD.11,34

***Effect of statin type***

In our cohort study, we also observed a consistent beneficial effect on the risk of clinical outcomes and liver stiffness progression for both lipophilic and hydrophilic statins. Lipophilic statins, such as simvastatin, fluvastatin, pitavastatin, lovastatin, and atorvastatin, can enter cells through passive diffusion and are present in various tissues.35 Conversely, hydrophilic statins, including rosuvastatin and pravastatin, require a liver-specific, carrier-mediated mechanism for their uptake. Therefore, lipophilic statins are believed to have more pleiotropic effects on non-lipid tissues.35,36 Lipophilic statins may stimulate antitumor immunity more efficiently compared to hydrophilic statins. They may also have antitumor effects by inducing G0/G1 cell cycle arrest, inhibiting Ras/Raf/Mek/ERK signaling, and promoting apoptosis in preclinical studies.24,37 A meta-analysis examining individual types of statins found that rosuvastatin, a hydrophilic statin, was associated with the most significant reduction in the risk of developing HCC.16

***Balance between potential risk and benefit of statin usage***

Physicians should be cautious when prescribing statins to patients with MASLD, even though statin usage is safe and may significantly reduce serum aminotransferase levels without any increased risk of hepatotoxicity.38 The most common side effects of statins are statin-associated muscle symptoms (SAMS), which include muscle pain, weakness, and even rhabdomyolysis.39,40 Extensive clinical experience with the widespread use of statins has shown that the risk of statin-induced severe liver injury is low, occurring in less than 1.2 out of 100,000 users, and is likely idiosyncratic.11,41 The statin benefits generally outweigh the potential risks. There is evidence to suggest that statins may lower the risk of liver stiffness progression, LREs, and mortality among patients with or without compensated cirrhosis.11,41 This evidence, combined with the known safety and tolerability of statins and their potential to reduce HCC risk, may lead hepatologists/gastroenterologists to consider using statins to improve clinical outcomes for cACLD or cirrhosis without incurring significant additional costs. However, these promising results will be best confirmed by large RCTs with long follow-up duration that evaluate the use of statins at baseline versus on-trial in patients with MASLD to minimize potential confounders.

***Limitations***

Our study has several limitations that should be mentioned. First, when patients are assessed at different intervals, it can affect the interpretation of the data. However, we looked at changes in non-invasive testing and clinical outcomes after VCTE examinations, considering intervals. Second, although we had a sufficient sample size for evaluating clinical outcomes, the 3-year median follow-up may be considered short, given the prolonged progression of chronic liver disease to cirrhosis and complications. Third, although we adjusted for potential confounders in our cohort study, the results might have overestimated the benefits of statins due to possible residual confounding in statin users. Differences between groups that we could not fully account for (confounding by indication) likely exist. This is a well-known issue in observational studies. Therefore, there is a need for long-term phase 3 RCTs to better evaluate the association between statin exposure and the risk of liver stiffness progression, LREs and mortality in patients with chronic liver diseases. Fourth, the intrinsic limitations of our database make it difficult to thoroughly study the complexities of drug interactions, especially between statins and glucose-lowering drugs, despite adjusting for antidiabetic drug use in the analysis. Fifth, our analysis included statin use as a time-dependent variable. However, patients had to have received at least 30 cDDD of statin therapy before being classified as "statin users", the index date was set only after this classification, potentially leading to immortal time bias. Last, the data included in this study were from tertiary referral centers, so the prognostic performance of VCTE should be confirmed in a more general setting in the future.

**Conclusions**

This large observational multicenter prospective cohort study includes liver VCTE data at baseline and follow-up. The results of this cohort study suggest that statin usage may help reduce CVD morbidity and mortality rates and slow down liver stiffness progression in both cACLD and non-cALCD patients. Although this cohort study provides a reliable estimate of the risk between statin usage and adverse liver-related outcomes in people with MASLD, future long-term RCTs are needed to further confirm the findings.

**Author Contributions:**

Guarantor of the article: Zheng is identified as the guarantor. Zhou and Zheng had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Zhou, Yip, Petta, Bugianesi, Yoneda, Calleja, Newsome, Fan, Fournier, G. Wong, Nakajima, Asgharpour, Kim, V. Wong. Acquisition, analysis, or interpretation of data: Lin, Lee, Yip, Tsochatzis, Bugianesi, Yoneda, Zheng, Hagström, Boursier, Calleja, Goh, W. Chan, Gallego-Durán, Sanyal, De Lédinghen, Newsome, Castéra, Lai, Fournier, G. Wong, Pennisi, Armandi, Nakajima, Liu, Shang, Saint-Loup, Llop, Teh, Lara-Romero, Asgharpour, Mahgoub, M. Chan, Canivet, Romero-Gomez, Kim, Targher, Byrne, V. Wong, Zheng. Drafting of the manuscript: Zhou and Zheng. Critical review of the manuscript for important intellectual content: All authors. Statistical analysis: Zhou and Zheng. Administrative, technical, or material support: Zhou, Lee, Bugianesi, Yoneda, Zheng, Goh, Newsome, Lai, Fournier, G. Wong, Nakajima, Liu, Shang, Saint-Loup, Asgharpour, M. Chan, V. Wong, Zheng. Supervision: Zhou, Yip, Tsochatzis, Bugianesi, Yoneda, W. Chan, Newsome, G. Wong, Armandi, Nakajima, Llop, Romero-Gomez, Kim, V. Wong, Zheng.

**Conflicts of Interest Statement:** Dr Yip reported serving as an advisory committee member and a speaker for Gilead Sciences outside the submitted work. Dr Tsochatzis reported receiving personal fees as an advisory board member for Boehringer, Novo Nordisk, Pfizer, and Siemens; receiving speaker fees from Echosens, Novo Nordisk, and AbbVie outside the submitted work. Dr Hagström reported personal fees from AstraZeneca, personal fees from Bristol Myers-Squibb, personal fees from MSD, personal fees from Novo Nordisk, personal fees from Boehringer Ingelheim, personal fees from KOWA, and personal fees from GW Phara outside the submitted work, and grants from AstraZeneca, grants from Echosens, grants from Gilead Sciences, grants from Intercept, grants from MSD, grants from Novo Nordisk, and grants from Pfizer outside the submitted work. Dr Boursier reported receiving grants and personal fees from Echosens outside the submitted work. Dr Calleja reported receiving other from Echosens Clinical Trials during the conduct of the study; grants from Roche Pharma and other from Gilead Advisory Board outside the submitted work. Dr WK. Chan reported serving as consultant or advisory board member for Zuellig Pharma, Abbott, Roche, AbbVie, Boehringer Ingelheim, and Novo Nordisk; and a speaker for Novo Nordisk, Abbott, Echosens, Viatris, and Hisky Medical. Dr Sanyal reported receiving grants from Intercept, personal consulting fees from Gilead, grants from Merck, personal consulting fees from Pfizer, grants and personal consulting fees from Eli Lilly, grants and personal consulting fees from Novo Nordisk, Boehringer Ingelheim, Novartis, Histoindex, and stock options from Genfit, Tiziana, Durect, Inversago, and personal consulting fees from Genentech, ALnylam, Regeneron, Zydus, LG chem, Hanmi, Madrigal, Path AI, 89 Bio, and stock options from Galmed outside the submitted work. Dr De Lédinghen reported receiving nonfinancial support from Echosens during the conduct of the study. Dr Newsome reported receiving grants from Novo Nordisk, advisory board and personal consulting fees, honoraria for lectures and travel expenses from Novo Nordisk, personal consulting and advisory board fees from Boehringer Ingelheim, Gilead, Intercept, Poxel Pharmaceuticals, Bristol-Myers Squibb, Pfizer, MSD, Sun Pharma, Eli Lilly, Madrigal, GSK, and nonfinancial support for educational events from AiCME outside the submitted work. Dr Castéra reported receiving personal fees for consulting and speakers bureau from Echosens during the conduct of the study; personal consultancy fees from Boston pharmaceutical and Gilead, speaker bureau and consultancy personal fees from GSK, personal speaker bureau fees from Inventiva, personal consultancy fees from Madrigal, personal Consultancy fees from MSD and Novo Nordisk, personal consultancy fees from Pfizer, Sagimet, and Siemens Healthineers outside the submitted work. Dr Fournier reported being in the full-time employment of Echosens during the conduct of the study. Dr G. Wong reported receiving personal fees from Echosens during the conduct of the study; and grants from Gilead Sciences Research outside the submitted work. Dr M. Chan reported being employed in the full-time by employment of Echosens during the conduct of the study. Dr Romero-Gomez reported receiving personal fees from Echosens outside the submitted work. Dr Kim reported personal fees from Gilead Sciences, personal fees from GSK, personal fees from Bayer, personal fees from Eisai, personal fees from AbbVie, personal fees from Echosens, personal fees from MSD, personal fees from Bristol-Myers Squibb, and personal fees from AstraZeneca outside the submitted work, and grants from AbbVie, grants from Bristol-Myers Squibb, and grants from Gilead Sciences outside the submitted work. Dr V. Wong reported receiving personal speaker fees from Abbott, consultant and speaker fees from AbbVie, personal consultant fees from Boehringer Ingelheim, Echosens, Gilead Sciences, grants from Gilead Sciences, personal consultant fees from Intercept, Inventiva, Novo Nordisk, personal consultant fees from Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, personal speaker fees from Unilab, personal consultant fees from Visirna, and being a cofounder of Illuminatio outside the submitted work. CDB has received grant support from Echosens. No other disclosures were reported.

**Group Information:** The VCTE-Prognosis Study Group consists of the following authors: Arun J. Sanyal, MD (Virginia Commonwealth University), Atsushi Nakajima, MD (University of Yokohama), Elisabetta Bugianesi, MD (University of Torino), Emmanuel Tsochatzis, PhD (Royal Free Hospital), George Boon-Bee Goh, MD (Singapore General Hospital), Hannes Hagström, PhD (Karolinska University Hospital), Jérôme Boursier, MD (Angers University Hospital), José Luis Calleja, MD (Hospital Puerta de Hierro), Manuel Romero-Gomez, MD (University of Seville), Ming-Hua Zheng, MD (Wenzhou Medical University), Philip N. Newsome,MD (University of Birmingham), Salvatore Petta, PhD (University of Palermo), Seung Up Kim, PhD (Yonsei University School of Medicine), Victor de Lédinghen, MD (University of Bordeaux), Vincent Wai-Sun Wong, MD (The Chinese University of Hong Kong), and Wah-Kheong Chan, MD (University of Malaya).

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**Figure Legends**

**Figure 1.** Study participant flow.

*Abbreviations:* VCTE, vibration-controlled transient elastography; MASLD, metabolic-associated steatotic liver disease; cDDDd, cumulative defined daily dose; HCC, hepatocellular carcinoma.

**Figure 2.** Kaplan-Meier survival analysis of the incidence of clinical outcomes in the whole cohort of participants stratified by statin usage.

*Abbreviations:* LRE, liver-related clinical events.

**Figure 3.** Kaplan-Meier survival analysis of the incidence of liver stiffness changes in the whole cohort of participants stratified by statin usage.

*Abbreviations:* LRE, liver-related clinical events.

**Figure 4.** Kaplan-Meier survival analysis of the incidence of clinical outcomes and liver stiffness changes in the whole cohort of participants stratified by statin usage and cACLD.

*Abbreviations:* cACLD*,* compensated advanced chronic liver disease.

**Supplementary Figure 1.** (A) Changes in liver stiffness between baseline and following VCTE examinations; (B) Kaplan-Meier survival analysis of the incidence of clinical outcomes in the whole cohort by liver stiffness changes in patients with non-cALCD; (C) Kaplan-Meier survival analysis of the incidence of clinical outcomes in the whole cohort by liver stiffness changes in patients with cACLD.

*Abbreviations:* cACLD*,* compensated advanced chronic liver disease; LRE, liver-related clinical events

**Supplementary Figure 2.** Subgroup analysis (forest plot) for clinical outcomes and liver stiffness changes in the whole cohort of participants stratified by types of statin usage.

*Abbreviations:* LRE, liver-related clinical events.

**Supplementary Figure 3.** Subgroup analysis (Kaplan-Meier curves) for the incidence of clinical outcomes and liver stiffness changes in the whole cohort of participants stratified by types of statin usage.

*Abbreviations:* LRE, liver-related clinical events.

**Table Legends**

**Table 1.** Clinical characteristics of the whole cohort and stratified by statin usage.

**Table 2.** Rates of clinical outcomes stratified by statin usage.

**Table 3.** Cox regression models for clinical outcomes stratified by cACLD and statin usage.

**Table 4.** Cox regression models for liver stiffness change stratified by cACLD and statin usage.

**Supplementary Table 1.** Cox regression models for clinical outcomes stratified by cACLD and fibrosis change.

**Supplementary Table 2.** Rates of liver stiffness changes stratified by cACLD and statin usage.

**Supplementary Table 3.** Sensitivity analyses.

**Supplementary Table 4.** Clinical characteristics stratified by statin usage after propensity score matching.

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| **Table 1.** Clinical characteristics of the whole cohort stratified by statin usage. |
| **Characteristics** | **All** **(N=7,988)** | **No statin use (N=4,755)** |  **Statin use (N=3,233)** | **P-value** |
| Age (years) | 53.0 ± 13.7 | 50.5 ± 14.3 | 56.3 ± 12.0 | <0.001 |
| Female sex, n (%) | 4,649 (58.2%) | 2,786 (58.6%) | 1,863 (57.6%) | 0.390 |
| BMI (kg/m2)  | 27.6 ± 4.7 | 28.0 ± 5.1 | 27.0 ± 4.0 | <0.001 |
| Diabetes, n (%)  | 2,804 (35.1%) | 1,148 (24.1%) | 1,656 (51.2%) | <0.001 |
| Hypertension, n (%)  | 2,959 (37.0%) | 1,380 (29.0%) | 1,579 (48.8%) | <0.001 |
| ALT (IU/L)  | 36 (23, 61) | 39 (24, 67) | 32 (21, 52) | <0.001 |
| AST (IU/L)  | 30 (22, 46) | 32 (23, 48) | 28 (21, 42) | <0.001 |
| GGT (IU/L)  | 43 (26, 76) | 45 (28, 82) | 39 (24, 69) | <0.001 |
| Albumin (g/L)  | 44.7 ± 3.5 | 44.8 ± 3.6 | 44.5 ± 3.3 | <0.001 |
| Total bilirubin (μmol/L)  | 13.7 ± 7.5 | 13.9 ± 8.1 | 13.5 ± 6.6 | 0.040 |
| Platelet count (×109 /L)  | 241 ± 67 | 240 ± 70 | 242 ± 64 | 0.191 |
| Creatinine (µmol/L) | 71 (59, 82) | 71 (60, 81) | 71 (59, 83) | 0.745 |
| Fasting glucose (mmol/L) | 6.3 ± 1.8 | 5.9 ± 1.6 | 6.7 ± 2.0 | <0.001 |
| TC (mmol/L) | 4.9 ± 1.1 | 4.9 ± 1.0 | 4.7 ± 1.2 | <0.001 |
| HDL (mmol/L) | 1.2 ± 0.3 | 1.3 ± 0.4 | 1.2 ± 0.3 | <0.001 |
| LDL (mmol/L) | 2.9 ± 1.0 | 3.0 ± 0.9 | 2.8 ± 1.1 | <0.001 |
| Triglycerides (mmol/L) | 1.8 ± 1.3 | 1.8 ± 1.2 | 1.9 ± 1.3 | <0.001 |
| cACLD, n (%) | 1,375 (17.2%) | 994 (20.9%) | 381 (11.8%) | <0.001 |
| LSM, kPa (IQR) | 5.9 (4.6, 8.2) | 6.1 (4.6, 8.9) | 5.5 (4.4, 7.3) | <0.001 |
| CAP, dB/m (IQR) | 301 (273, 333) | 303 (273, 335) | 299 (273, 330) | 0.062 |
| *Abbreviations:* AST, alanine aminotransferase; AST, aspartate aminotransferase; BMI: body mass index; cACLD: compensated advanced chronic liver disease; CAP, controlled attenuation parameter; CI, confidence interval; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; HR, hazard ratios; LDL, Low-density lipoprotein; LRE, liver-related events; LSM, liver stiffness measurement; TC, total cholesterol. |

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| **Table 2.** Rates of all-cause death and liver-related outcomes stratified by statin usage. |
|  | **No statin use** | **Statin use** | **P-value** |
| Subjects, n (%) | 4755 (59.5%) | 3233 (40.5%) |  |
| Follow-up time, years | 4.2 (2.7, 6.4) | 5.0 (3.7 6.5) | <0.001 |
| All-cause death, n (%) | 68 (1.4%) | 19 (0.6%) | <0.001 |
| LRE, n (%) | 156 (3.3%) | 52 (1.6%) | <0.001 |
| HCC | 72 (1.5%) | 32 (1.0%) | 0.044 |
| Ascites | 65 (1.4%) | 9 (0.3%) | <0.001 |
| Spontaneous bacterial peritonitis | 4 (0.1%) | 4 (0.1%) | 0.722 |
| Variceal hemorrhage | 40 (0.8%) | 18 (0.6%) | 0.179 |
| Hepatic encephalopathy regression | 28 (0.6%) | 5 (0.2%) | 0.002 |
| Hepatorenal syndrome regression | 3 (0.1%) | 2 (0.1%) | 1.000 |
| Liver transplantation regression | 9 (0.2%) | 7 (0.2%) | 0.803 |
|  Liver related death | 20 (0.4%) | 0 (0%) | <0.001 |
| *Abbreviations:* HCC: hepatocellular carcinoma; LRE: liver-related events. |

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| **Table 3.** Cox regression models for adverse clinical outcomes stratified by cACLD and statin usage. |
|  | **Events in no-statin user** | **Events in statin user** | **Adjusted HR** | **P-value** |
| All |  |  |  |  |
| All-cause death | 68 (1.4%) | 19 (0.6%) | 0.233 (0.127 - 0.426) | <0.001 |
| LRE | 156 (3.3%) | 52 (1.6%) | 0.380 (0.268 - 0.539) | <0.001 |
| Non-cACLD |  |  |  |  |
| All-cause death | 28 (0.7%) | 15 (0.5%) | 0.262 (0.118 - 0.582) | <0.001 |
| LRE | 30 (0.8%) | 17 (0.6%) | 0.476 (0.243 - 0.930) | <0.001 |
| cACLD |  |  |  |  |
| All-cause death | 40 (4.0%) | 4 (1.0%) | 0.200 (0.068 - 0.593) | 0.004 |
| LRE | 126 (12.7%) | 35 (9.2%) | 0.562 (0.372 - 0.849) | <0.001 |
| Adjusted for age, sex, BMI, diabetes, hypertension, baseline LSM and baseline CAP.*Abbreviations:* BMI, body mass index; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; CI, confidence interval; HR, hazard ratios; LRE, liver-related events; LSM, liver stiffness measurement.  |

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| **Table 4.** Cox regression models for liver stiffness change stratified by cACLD and statin usage. |
|  | **No Statin use** | **Unadjusted HR****(95% CI)** | **P-value** | **Adjusted HR****(95% CI)** | **P-value** |
| All |  |  |  |  |  |
| Liver stiffness progression | *Ref.* | 0.499 (0.412 - 0.604) | <0.001 | 0.411 (0.333 - 0.508) | <0.001 |
| Non-cACLD |  |  |  |  |  |
| Liver stiffness progression | *Ref.* | 0.688 (0.507 - 0.933) | 0.016 | 0.450 (0.342 - 0.592) | <0.001 |
| cACLD |  |  |  |  |  |
| Liver stiffness progression | *Ref.* | 0.523 (0.408 - 0.670) | <0.001 | 0.542 (0.389 - 0.755) | <0.001 |
| Liver stiffness regression | *Ref.* | 1.052 (0.906 - 1.222) | 0.504 | 0.914 (0.778 - 1.074) | 0.275 |
| Adjusted for age, sex, BMI, diabetes, hypertension, baseline LSM and baseline CAP.*Abbreviations:* BMI, body mass index; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; CI, confidence interval; HR, hazard ratios; LSM, liver stiffness measurement. |