Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Meta-Analysis

Statins in chronic liver disease and its complications: An umbrella review and meta-analysis of systematic reviews

Filippo Cattazzo[a,b], Felice Cinque[c,d,1], Vincenzo Di Maria[a], Marco Vicardi[a,b], Anna Mantovani[a,b], Mirko Zoncapè[a,b], Leonardo Antonio Natola[a,b], David Sacerdoti[b], Rosa Lombardi[c,d,2], Andrea Dalbeni[a,b,2,*]

[a] Department of Medicine, Medicine C, University of Verona and Hospital Trust of Verona (Azienda Ospedaliera Universitaria AOUI), Verona, Italy.
[b] Liver Unit, Department Medicine, University of Verona, Verona, Italy
[c] Medicina Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan Italy.
[d] Department of Pathophysiology and Transplantation, University of Milan, Milan Italy.

ARTICLE INFO

Article history:
Received 30 March 2026
Accepted 20 May 2026
Available online xxx

Keywords:
Hepatocellular carcinoma
Hepatic Decompensation
Meta-analysis
Mortality
Statins

ABSTRACT

Background and aims: Statins have been proposed as hepatoprotective agents in chronic liver disease (CLD); however, evidence from existing systematic reviews—including observational studies and clinical trials—is inconsistent and affected by substantial overlap. We conducted an umbrella review to synthesize the available evidence on the associations between statin use and hepatological outcomes in CLD patients, while addressing study overlap.

Design: PubMed, EMBASE, and Cochrane Library were searched up to September 2025 for systematic reviews of statin therapy in CLD. Methodological quality was evaluated using AMSTAR-2. Study overlap was assessed using corrected covered area (CCA) and minimized via hierarchical exclusion prioritizing methodological quality, comprehensiveness, and recency. Random-effects meta-analyses with bias assessments were conducted.

Results: Of 850 records screened, 17 systematic reviews (229 unique studies; 10,515,877 participants from 34 countries) were included after overlap adjustment (CCA = 5.79%). Statin therapy was associated with 46% reduction in hepatocellular carcinoma (HCC) risk (HR 0.54, 95% CI 0.48–0.59; I^2 = 46.7%) and 46% reduction in hepatic decompensation (HR 0.54, 95% CI 0.49–0.59; I^2 = 0.1%); these estimates derive predominantly from observational studies and should be interpreted as associations rather than causal effects. Geographic heterogeneity was observed: Asian populations showed stronger benefits (HCC HR 0.49, 95% CI 0.45–0.53; I^2 = 0%) compared with Western populations (HCC HR 0.71, 95% CI 0.52–0.96; I^2 = 95.7%; p = 0.003). Statin use also associated with reduced all-cause mortality (HR 0.65, 95% CI 0.52–0.81), though with substantial heterogeneity (I^2 = 80%). In contrast, available RCT-based evidence does not consistently confirm these associations for decompensation or mortality outcomes.

Conclusions: Statin use is consistently associated with reduced HCC risk and hepatic decompensation in CLD patients, particularly in Asian populations, though these findings derive predominantly from observational evidence subject to potential confounding. These associations support the continued use of statins in patients with CLD and cardiovascular indications where these are otherwise indicated, with potential additive hepatoprotective effects. These results underscore the urgent need for adequately powered randomized trials to clarify the boundaries of safety and efficacy in this high-risk population.

1. Introduction

Cirrhosis represents a major global health burden, causing more than 1.32 million deaths globally in 2017, with deaths due to cirrhosis constituting 2.4% of total deaths worldwide, compared with 1.9% in 1990 [1]. Despite therapeutic advances, the complications of advanced liver disease—including portal hypertension,

* Corresponding author.
E-mail address: andrea.dalbeni@aovr.veneto.it (A. Dalbeni).
[1] Equally contributed to the work.
[2] co-last authors.

https://doi.org/10.1016/j.dld.2026.05.010

variceal bleeding, hepatocellular carcinoma (HCC), and acute-on-chronic liver failure (ACLF)—remain challenging to manage [2]. The potential role of statins in liver disease has generated considerable interest, though also substantial controversy. Initially, clinicians were reluctant to prescribe these medications in patients with liver disease due to concerns about hepatotoxicity. This paradigm began shifting in the early 2000s when observational studies suggested that statins might actually confer hepatoprotective benefits in chronic liver disease (CLD) [3]. The pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors extend well beyond cholesterol reduction, encompassing anti-inflammatory, antioxidant, and antifibrotic properties that could theoretically benefit patients with chronic liver disease [4–6]. These mechanisms include inhibition of the mevalonate pathway, which reduces isoprenoid intermediate availability essential for cellular proliferation and inflammatory processes [7]. Additionally, statins enhance endothelial nitric oxide synthase activity, promoting vasodilation and reducing intrahepatic vascular resistance [8]. The anti-inflammatory effects are mediated through downregulation of nuclear factor-κB signalling and reduction in C-reactive protein levels [9]. Furthermore, statins demonstrate antifibrotic properties by inhibiting hepatic stellate cell activation and reducing collagen synthesis [10]. However, the evidence base remains fragmented and sometimes contradictory. Whilst some large cohort studies have demonstrated impressive reductions in HCC incidence and liver-related mortality among statin users [11–13], others have found more modest or non-significant effects [14,15]. The heterogeneity in study populations, statin types, dosing regimens, and outcome definitions has made it difficult for clinicians to draw definitive conclusions about the role of these medications in cirrhotic patients. The proliferation of systematic reviews addressing this question presents both an opportunity and a challenge. Multiple reviews often examine overlapping primary studies, potentially leading to misleading conclusions if not properly synthesised [16]. Furthermore, the methodological quality of these reviews varies considerably, from rigorous analyses that follow international guidelines to more limited syntheses with significant methodological shortcomings [17]. We therefore conducted this umbrella review to provide the most comprehensive synthesis of the available systematic review and meta/analytic evidence on statin therapy in CLD, with particular attention to methodological quality, study overlap, and clinical applicability. Our objective was not merely to aggregate existing meta-analyses, but to critically evaluate the consistency and reliability of findings across multiple independent research groups, identify areas of true consensus versus persistent uncertainty, and provide clinically meaningful guidance for hepatologists.

2. Material and methods

The protocol was prospectively registered with PROSPERO (CRD420251131230). A comprehensive search strategy was developed in collaboration with an experienced medical librarian and refined through pilot searches. The strategy combined controlled vocabulary terms (MeSH for PubMed, Emtree for EMBASE) with carefully selected free-text terms, accounting for variations in terminology across different geographical regions and time periods.

2.1. Search strategy

2.1.1. PubMed search strategy (adapted for other databases)

("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR statin*[tiab] OR atorvastatin[tiab] OR simvastatin[tiab] OR pravastatin[tiab] OR rosuvastatin[tiab] OR lovastatin[tiab] OR fluvastatin[tiab] OR pitavastatin[tiab])

AND

("Liver Fibrosis" [Mesh] OR "Liver Cirrhosis"[Mesh] OR "Hypertension, Portal"[Mesh] OR "Carcinoma, Hepatocellular"[Mesh] OR "Acute-On-Chronic Liver Failure"[Mesh] OR fibrosis[tiab] OR cirrhosis[tiab] OR cirrhotic[tiab] OR "portal hypertension"[tiab] OR hepatocellular carcinoma[tiab] OR HCC[tiab] OR "liver decompensation"[tiab] OR ACLF[tiab]) OR mortality[tiab] OR death[tiab] OR survival[tiab]

AND

("Meta-Analysis"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR "Systematic Review"[Publication Type] OR "systematic review"[tiab] OR meta-analys*[tiab] OR metaanalys*[tiab])

Search filters were applied to exclude animal studies, case reports, and conference abstracts. No language restrictions were imposed initially, with non-English articles assessed by native speakers or professional translation services when abstracts suggested potential relevance.

2.2. Study selection and inclusion criteria

Three investigators (FC, MV and FC) independently screened titles, abstracts, and full texts for eligibility. Disagreements were resolved through consensus or consultation with a third reviewer. Studies were included if they met the following criteria:

- Study design: Systematic reviews with or without meta-analysis
- Population: Patients with chronic liver disease (CLD) or cirrhosis of all aetiologies
- Intervention: Any statin therapy (regardless of type, dose, or duration)
- Outcomes: HCC incidence, hepatic decompensation, ACLF, mortality, portal hypertension, variceal bleeding, or safety outcomes
- Publication: Peer-reviewed articles in scientific journals

Exclusion criteria: narrative reviews, editorials, conference abstracts, case reports, individual observational studies or randomised controlled trials, and reviews focusing exclusively on non-cirrhotic populations.

2.3. Data extraction

Data extraction was performed by three independent reviewers (FC, MV and FC) using a standardised form. Extracted information included: first author details, publication year, search dates, number and design of included studies, population characteristics, statin types and dosing, follow-up duration, outcome measures, effect estimates with confidence intervals, measures of heterogeneity, and quality assessment results. For each included review, we additionally recorded whether the primary studies were predominantly observational, predominantly randomized controlled trials (RCTs), or mixed, in order to facilitate stratified interpretation of pooled estimates.

2.4. AMSTAR-2 quality assessment

The methodological quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) tool [18]. AMSTAR-2 evaluates 16 domains of systematic review methodology, with seven critical domains identified: protocol registration prior to commencement, adequacy of literature search, justification for excluding individual studies, risk of bias assessment, appropriateness of meta-analytical methods, consideration of risk of bias when interpreting results, and assessment of publication bias. Three reviewers (FC, MV and FC) independently assessed each systematic review, with discrepancies resolved through discussion. Overall confidence was classified as high (AMSTAR-2 $\geq$12), moderate (8-11), low (5-7), or critically low ($<$5).

2.5. Assessment of overlapping reviews

Given the potential for multiple systematic reviews to include overlapping primary studies, we assessed the degree of overlap using the corrected covered area (CCA) method [19]. CCA was calculated as: CCA = (N - r) / (r × c - r), where N represents the total number of publications appearing in at least one systematic review, r represents the number of systematic reviews, and c represents the number of unique primary studies. CCA values were interpreted as: 0-5% (slight overlap), 6-10% (moderate overlap), 11-15% (high overlap), and >15% (very high overlap). For reviews with high overlap (>15%), we implemented a hierarchical exclusion strategy prioritising: methodological quality (AMSTAR-2 score), comprehensiveness of search strategy, recency of publication, and sample size of included studies.

2.6. Statistical analysis

Meta-analysis was performed using the meta for package in R employing random-effects models with REML estimation to account for anticipated heterogeneity between studies. Effect sizes were expressed as hazard ratios (HR), Relative Risk (RR), Rate Difference (RD), odds ratios (OR), or mean differences (MD) with 95% confidence intervals. Where reviews reported different effect measures for the same outcome, pooled analyses were restricted to those reporting the same metric; reviews reporting different measures were described narratively and included in the structured comparison of observational versus RCT evidence. Statistical heterogeneity was assessed using the I^2 statistic [20], with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. In cases of substantial heterogeneity (I^2 >50%), we explored potential sources through subgroup analyses based on geographic region (Asia vs Western countries). Additional subgroup analyses stratifying reviews by primary study design (observational/mixed vs RCT-only) were performed for decompensation and mortality outcomes. Publication bias was evaluated using funnel plot visual inspection and Egger's regression test when ≥10 studies were available [21], hence it couldn't be performed for HCC prevention, hepatic decompensation, and all-cause mortality analyses. A post-hoc sensitivity analysis was performed restricting the decompensation and mortality analyses to reviews that included exclusively or predominantly cirrhotic populations, in order to explore the potential impact of disease severity on observed associations. Sensitivity analyses were conducted using leave-one-out analysis to assess the influence of individual studies. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant.

3. Results

Our comprehensive search identified 1,262 records. After removing duplicates, 850 unique records were screened. Following rigorous screening, 65 full-text articles were assessed for eligibility. Of these, 21 were excluded as they were primary studies, narrative reviews, or duplicate umbrella reviews. Consequently, 44 systematic reviews initially met inclusion criteria. However, overlap assessment revealed a critical methodological challenge: the initial CCA indicated very high overlap between reviews. After implementing our hierarchical exclusion strategy prioritising methodological quality whilst maintaining population representativeness, we excluded 27 of the 44 overlapping reviews. This successfully reduced the CCA to an acceptable 5.79%, resulting in 17 systematic reviews included in the final synthesis (Fig. 1).

Following full-text assessment, 21 articles were excluded as they were primary studies, narrative reviews, or duplicate umbrella reviews (Supplementary Table S1). Of the remaining 44 systematic reviews eligible for synthesis, 27 were subsequently excluded due to high overlap (>5% CCA) or lower methodological quality to minimize redundancy.

Specifically, reviews were retained based on: (1) highest AMSTAR-2 score within overlapping sets; (2) most comprehensive search strategy when scores were equal; (3) most recent publication date when both quality and comprehensiveness were comparable; and (4) largest sample size as the final criterion. This systematic approach ensured that the most methodologically rigorous and comprehensive evidence was retained while minimizing redundancy. The PRISMA flowchart is depicted in Fig. 1.

The final analysis included 17 systematic reviews encompassing 229 unique primary studies with 10,515,877 participants from 34 countries. AMSTAR-2 quality assessment demonstrated variable methodological rigour: three reviews achieved high quality (≥12 points), twelve reached moderate quality (8-11 points), and two were rated as low quality (5–7 points). No included review was rated critically low (Table 1).

The 17 included systematic reviews with meta-analysis showed considerable diversity in scope and population characteristics. Geographic distribution was broad, with studies from Asia-Pacific regions, North America, Europe, and mixed international cohorts. Population characteristics varied substantially, encompassing viral hepatitis, metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD), mixed aetiologies, and portal hypertension-specific populations. Of note, the majority of primary studies included across reviews were observational in design; only two included reviews (Abdulrazzak et al. and Zhang et al. 2022) were based exclusively on RCTs, and both contributed limited sample sizes compared with the observational evidence base (Table 1).

3.1. Primary outcomes

3.1.1. Hepatocellular carcinoma prevention

Six systematic reviews contributed to the HCC prevention analysis [12,13,15,31,33,34], representing studies with participants from multiple countries (Fig. 2). Statin therapy was associated with a statistically significant 46% reduction in HCC risk (HR 0.54, 95% CI 0.49-0.59, $p<0.001$). The heterogeneity was moderate ($I^2=36.5\%$), suggesting reasonable consistency across studies. Importantly, all six reviews included in the HCC analysis were based on observational or mixed study designs. No reviews of randomised controlled trials (RCT) were available for this outcome, precluding a formal subgroup analysis by study design.

The most striking finding was the significant geographic heterogeneity (Fig. 3). Asian populations showed a strong and homogeneous association (HR 0.49, 95% CI 0.45-0.53, $I^2=0.0\%$), whilst Western populations demonstrated a more modest association with extremely high heterogeneity (HR 0.70, 95% CI 0.54-0.89, $I^2=92.5\%$). The test for subgroup differences was statistically significant ($p=0.003$), indicating that geographic region is an important modifier of the statin-HCC association. Publication bias assessment using funnel plot inspection showed no obvious asymmetry (Supplementary Fig. 1 panel A).

3.2. Hepatic decompensation

Four systematic reviews contributed to the decompensation analysis [11,26–28], revealing a significant 46% reduction in risk (HR 0.54, 95% CI 0.49-0.59, $p<0.001$, $I^2=0.1\%$) (Fig. 4).

The near-absence of heterogeneity suggests a remarkably consistent association across different populations and study designs. However, subgroup analysis by study design revealed important differences. The four reviews based on observational or mixed studies showed a strong association with minimal heterogeneity (HR 0.54, 95% CI 0.49-0.59, $I^2=0.1\%$). In contrast, one additional

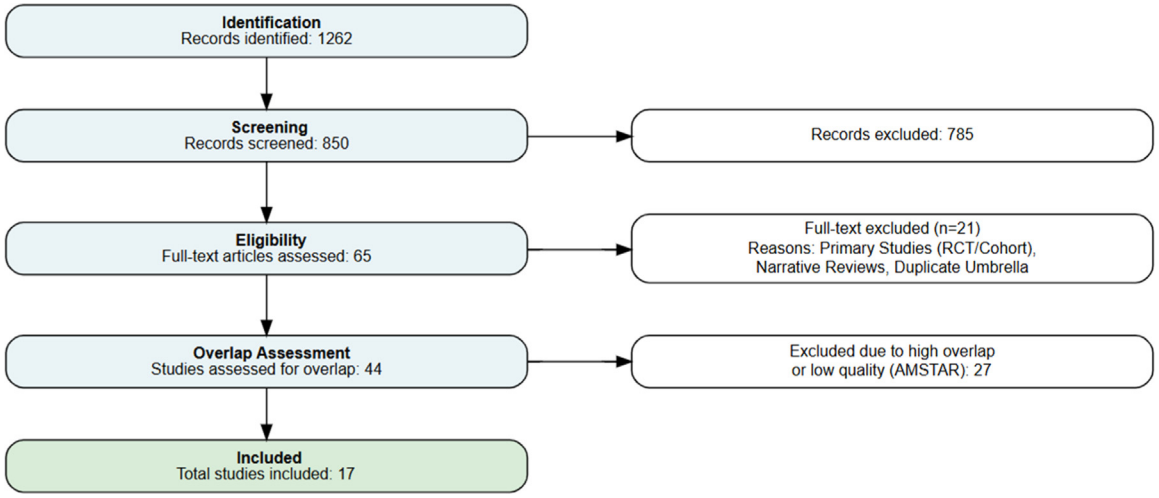

Fig. 1. PRISMA flow chart.

Table 1
Characteristics of systematic reviews/metanalysis included in the analysis.

First Author	Year	N° Studies Included	N° Participants	Population	Primary Outcome	AMSTAR-2	Primary Study Design	CCA Contribution
Ayada et al. [22]	2023	7	5145	MASLD	Fibrosis & NASH risk	9	Observational	0,15
Abdulrazzak et al. [23]	2025	6	492	Cirrhosis	Portal Pressure (HVPG)	12	RCTs Only	0,92
Boutari et al. [24]	2022	13	789	NAFLD	Histology & Enzymes (NAFLD)	9	Observational	0,49
Fatima et al. [25]	2022	14	1247503	NAFLD	Histology & Enzymes (NAFLD)	9	Observational	0,63
Gu et al. [26]	2019	17	195602	Cirrhosis	Mortality, Decompensation, HCC	11	Observational & Mixed	3,01
Kamal et al. [11]	2017	17	158172	Mixed CLD	HCC, decompensation, mortality	12	Observational & Mixed	2,38
Kim et al. [27]	2017	13	121058	Mixed CLD/Cirrhosis	Decompensation, Mortality	11	Observational & Mixed	3,06
Li et al. [13]	2022	10	548073	Viral Hepatitis	HCC prevention	10	Observational	1,56
Ma et al. [28]	2017	10	123445	Viral Hepatitis	Cirrhosis & Decompensation	10	Observational	2,09
Sung et al. [29]	2021	22	2781	Cirrhosis	Pharmacokinetics & Safety	8	Observational	1,46
Vahedian-Azimi et al. [30]	2021	9	195602	Viral Hepatitis	Multiple outcomes	9	Observational & Mixed	2,09
Wong et al. [12]	2021	12	89451	Mixed CLD	HCC prevention	11	Observational	1,94
Wang et al. [31]	2022	32	4963518	Mixed CLD	HCC prevention	11	Observational	2,09
Zhang et al. [32]	2022	9	648	Cirrhosis	Mortality, Bleeding	10	RCTs Only	1,31
Zhang et al. [15]	2023	5	684363	NAFLD	HCC Risk	10	Observational	0,15
Zeng et al. [33]	2023	10	1774476	Mixed CLD	HCC chemoprevention	12	Observational	1,02
Zheng et al. [34]	2017	23	404759	HCV	SVR, HCC, Cirrhosis	10	Observational & Mixed	3,01

Legend: CLD: chronic liver disease; NALFD=non-alcoholic fatty liver disease; NASH=non-alcoholic steatohepatitis; MASLD: metabolic-dysfunction associated steatotic liver disease, SVR=sustained virological response.

review by Abdulrazzak et al. [23] that included only RCTs, which could not be pooled due to reporting a different effect measure (Risk Difference), found no statistically significant association with decompensation (Risk Difference 0.03, 95% CI -0.08 to 0.13). Publication bias assessment using funnel plot inspection showed no obvious asymmetry (Supplementary Fig. 1 panel B).

3.3. All-cause mortality

Five systematic reviews provided mortality data suitable for meta-analysis [11,25,26,29,30] (excluding Abdulrazzak et al. [23] which reported Risk Difference). All-cause mortality showed an association with 38% reduction (HR 0.62, 95% CI 0.51-0.77, $p<0.001$), though with substantial heterogeneity ($I^2=77.4\%$). This high heterogeneity suggests important differences between studies that warrant cautious interpretation. To explore the impact of study design on mortality outcomes, we conducted a subgroup analysis stratifying reviews by the type of primary studies included (Fig. 5). The four reviews based on observational or mixed studies [11,26,27,30] showed a significant association between statin use and reduced mortality, albeit with considerable heterogeneity (pooled HR 0.65, 95% CI 0.52-0.81, $I^2=80.0\%$) (Supplementary Fig. 2).

Zhang et al. [32], based exclusively on RCTs, reported a pooled RR of 0.46 (95% CI 0.29–0.73, $I^2=0.0\%$); the test for subgroup differences between observational and RCT-based reviews was not statistically significant ($p=0.269$).

3.4. Sensitivity analyses

Leave-one-out sensitivity analysis for HCC prevention demonstrated remarkable stability of the pooled estimate (Supplementary Table 2, Supplementary Fig. 3).

Sequential exclusion of each review yielded HRs ranging from 0.58 to 0.64, all remaining statistically significant. This consis-

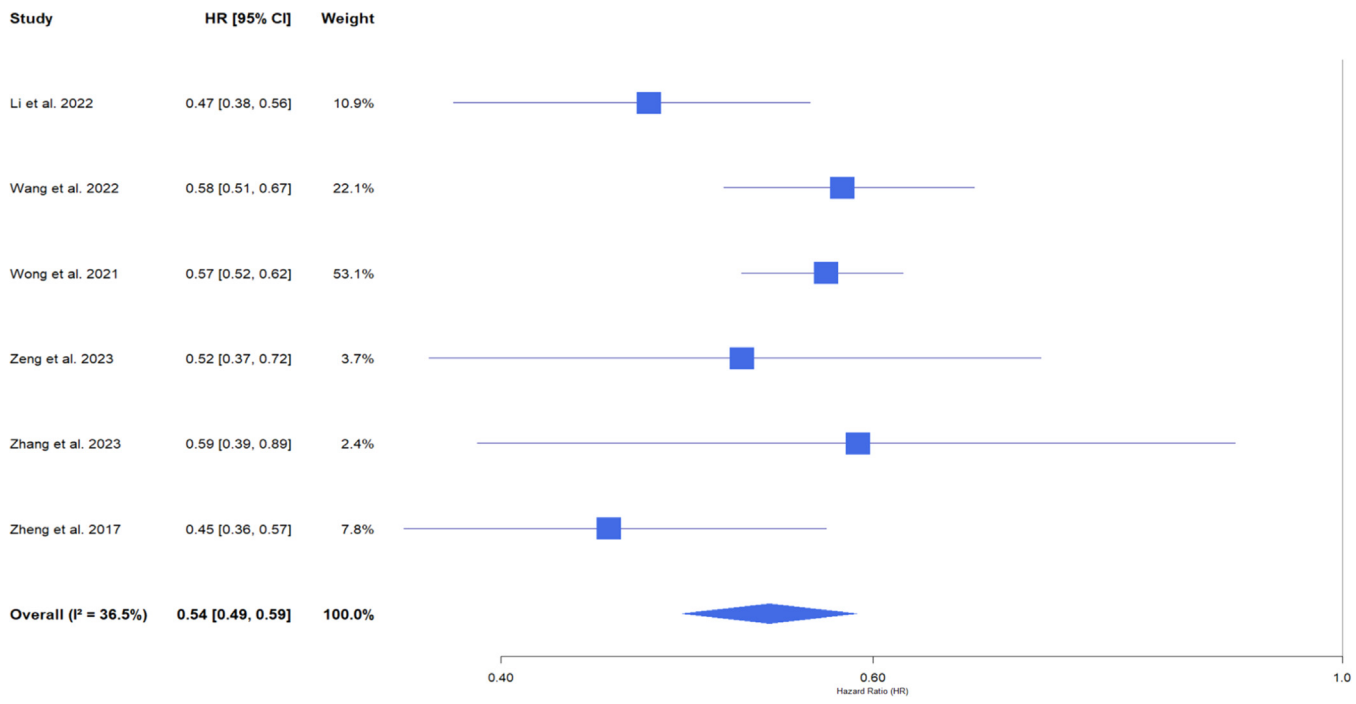

Fig. 2. Forest plot HCC prevention.

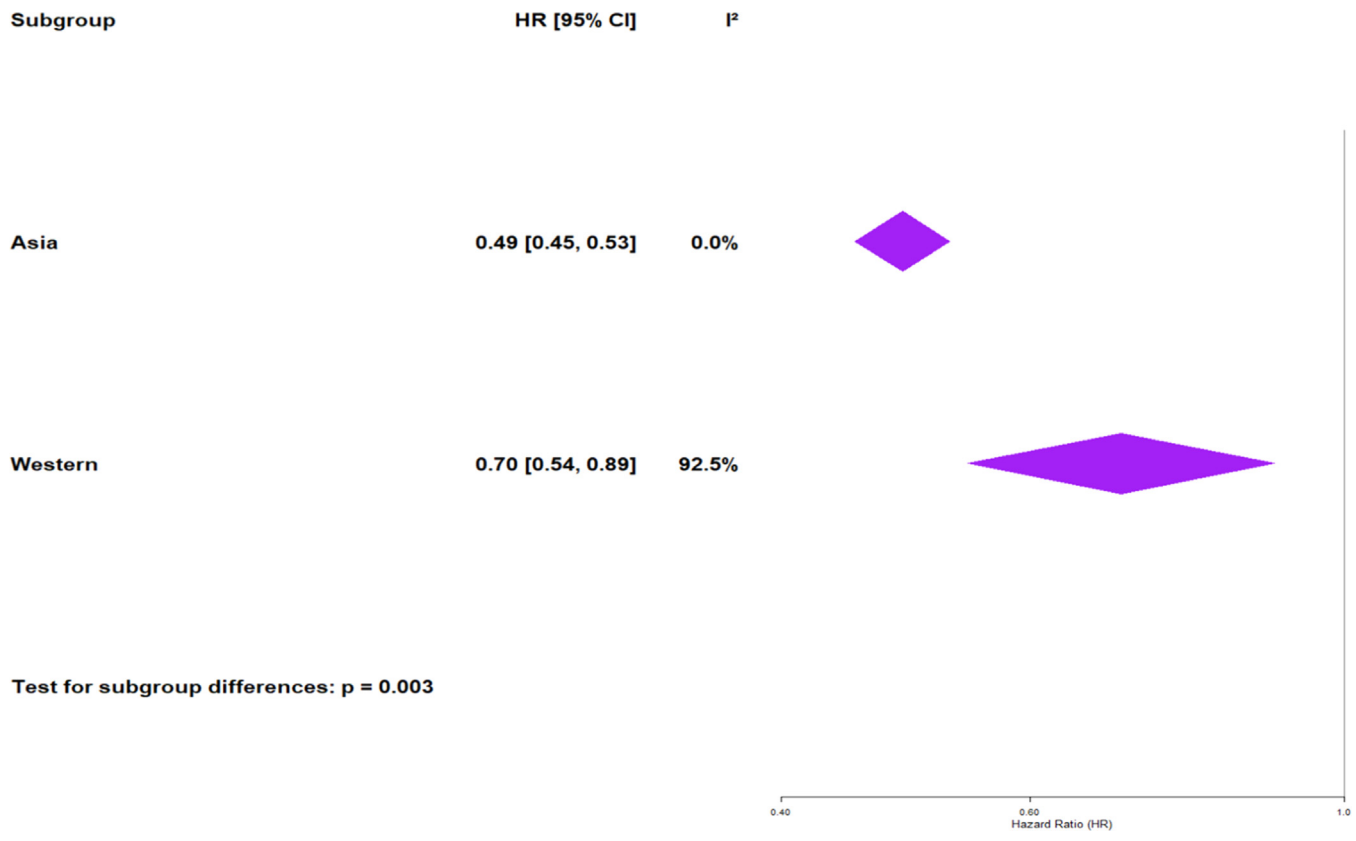

Fig. 3. Forest plot for geographic subgroups.

tency strengthens confidence in the robustness of the HCC prevention association. Meta-regression analysis examining the relationship between study quality (AMSTAR-2 score) and effect size showed no significant association (Supplementary Fig. 4), suggesting that the observed associations are not merely artefacts of lower-quality studies. The Galbraith plot for HCC prevention (Supplementary Fig. 5) demonstrates a high degree of consistency among the included meta-analyses. Most studies fall within the 95% confidence bounds (shaded area), indicating that the variability in the reported hazard ratios is largely due to sampling error rather than significant clinical or methodological heterogeneity. This visual confirmation aligns with the moderate I^2 value

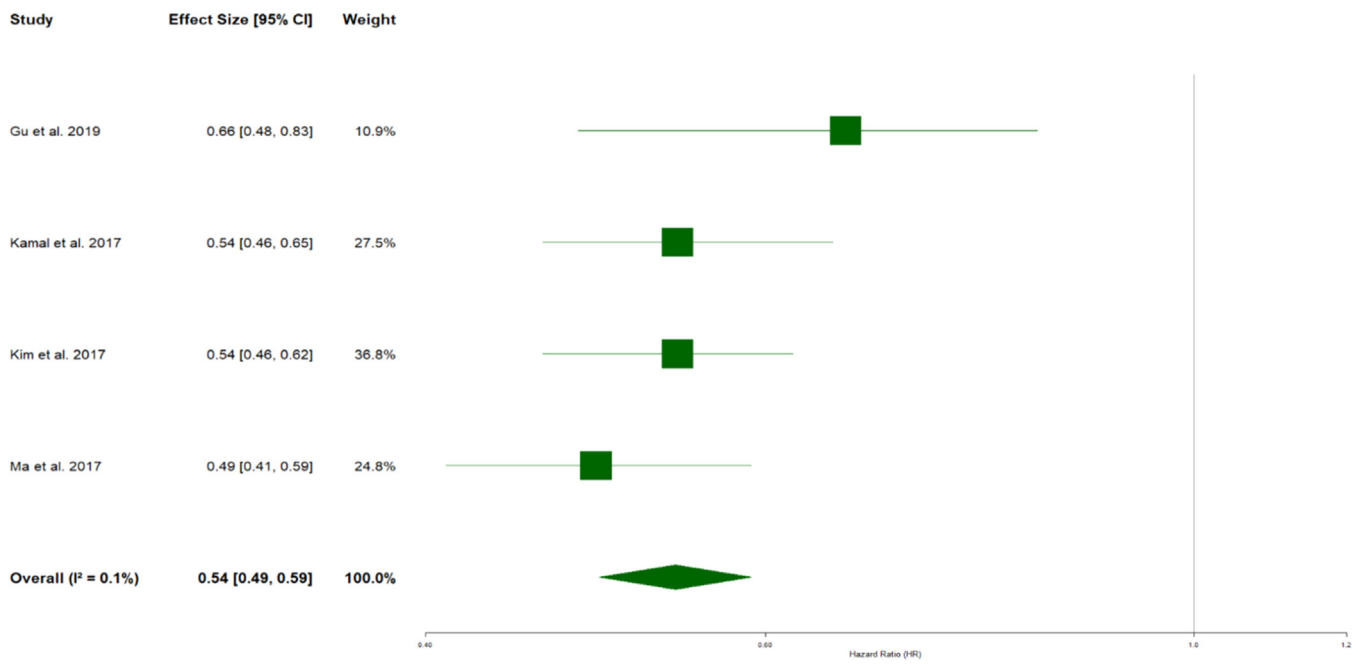

Fig. 4. Forest plot hepatic decompensation.

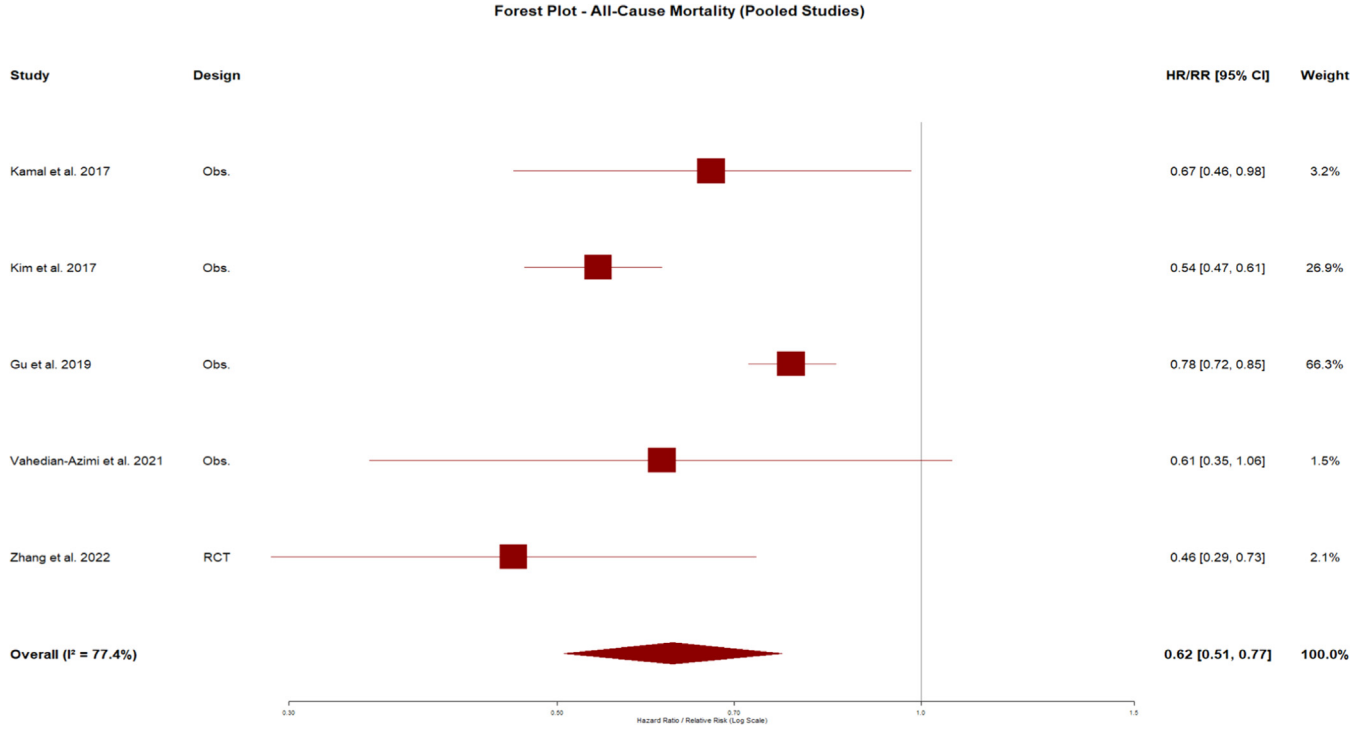

Fig. 5. Forest plot all-cause mortality.

(36.5%) and strengthens the validity of the pooled association estimate.

Post-hoc sensitivity analysis restricting decompensation and mortality analyses to reviews that included exclusively or predominantly cirrhotic populations (Gu et al. 2019, Kamal et al. 2017, Kim et al. 2017, Zhang et al. 2022, Abdulrazzak et al. 2025) showed results consistent with the main analysis for decompensation (HR 0.56, 95% CI 0.50–0.62).

For mortality, the restricted analysis similarly yielded a significant reduction in risk with persistent high heterogeneity (HR 0.62, 95% CI 0.49–0.79, $I^2 = 83.9\%$). Formal stratification by cirrhosis severity (compensated vs decompensated) was not feasible at the level of aggregate data from systematic reviews, as most included reviews did not consistently separate these populations.

3.5. Safety Outcomes

Safety data were available from 7 systematic reviews. Hepatotoxicity rates were generally low, suggesting that statins can be safely used in compensated cirrhosis with appropriate monitoring. However, muscle-related adverse events showed divergence based on study design. Large observational cohorts reported no signifi-

cant risk of myopathy (Wong et al. [12]: **HR 1.07**, 95% CI 0.91–1.27). In contrast, meta-analyses of RCTs suggested a potential safety signal: Zhang et al. [32] reported a pooled Relative Risk (RR) for asthenia/myalgia of 1.65 (95% CI 0.93–2.95), and Abdulrazzak et al. [23] highlighted dose-dependent toxicity, particularly noting risks associated with simvastatin 40 mg (Supplementary Table 3).

4. Discussion

This umbrella review provides a comprehensive synthesis of the available evidence on statin use in CLD including cirrhosis, demonstrating consistent associations between statin therapy and reduced risks of HCC and hepatic decompensation. The observed 46% relative risk reduction for both outcomes is numerically striking; however, these estimates derive predominantly from observational studies and their interpretation requires careful consideration of the methodological limitations inherent to this evidence base, as detailed below. This clinical evidence might be explained by several biological mechanisms. Statins enhance intrahepatic nitric oxide bioavailability through endothelial nitric-oxid-synthase upregulation, reduce hepatic stellate cell activation via Rho kinase suppression [35], and attenuate oxidative stress through upregulation of antioxidant enzymes [36], collectively lowering portal pressure and improving hepatic function. They also inhibit the mevalonate pathway, decreasing the availability of isoprenoid intermediates essential for tumor proliferation [37] and reduce Ras and Rho signaling, both critical drivers of cellular transformation and metastasis [38]. Additionally, statins promote pro-apoptotic activity through p53 pathway activation and exert anti-angiogenic effects by VEGF downregulation [39]. Their anti-inflammatory effects – mediated by reduced nuclear factor-κB activation and cytokine production - further create an inhospitable microenvironment for hepatocarcinogenesis [40]. These plausible biological mechanisms lend biological credibility to the observed associations, but do not substitute for causal evidence from randomized trials. The consistency of associations across multiple independent research groups provides some degree of epidemiological coherence [41], but cannot rule out the presence of systematic biases common to the observational literature.

4.1. Observational evidence versus RCT evidence

A structured comparison of the available evidence by study design reveals an important and clinically meaningful divergence. Observational and mixed-design reviews consistently report large protective associations for decompensation (HR ~0.54) and mortality (HR ~0.62–0.65). In contrast, the two RCT-based reviews included in this analysis tell a more nuanced story: Zhang et al. [32], reporting on simvastatin in cirrhosis, found a mortality benefit (RR 0.46, 95% CI 0.29–0.73) without statistical heterogeneity, suggesting potential efficacy in a selected cirrhotic population. However, Abdulrazzak et al. [23], pooling RCTs that measured decompensation and mortality as primary endpoints, found no statistically significant benefit for either outcome (RD 0.03, 95% CI -0.08 to 0.13 for decompensation; RD -0.02, 95% CI -0.10 to 0.05 for mortality). The latter review included only 492 participants, substantially limiting its statistical power. The discrepancy between observational and RCT findings is consistent with the known impact of immortal time bias, confounding by indication, and healthy user bias in observational hepatology research, all of which tend to inflate apparent treatment benefits. Until adequately powered, well-designed RCTs report their findings — particularly the ongoing SACRED trial [42], which is evaluating simvastatin in approximately 2,400 patients with compensated high-risk cirrhosis — causal inference from the current evidence base remains premature.

Despite the consistency of the observed associations, important concerns arise from the geographic heterogeneity, especially in HCC prevention, where the association appears stronger in Asian populations (HR 0.49, I^2=0%) than in Western cohorts (HR 0.70, I^2=92.5%). Several factors may account for this discrepancy: (1) differences in cirrhosis etiology, with hepatitis B virus (HBV) predominating in Asia versus alcohol and MASLD in Western countries; (2) genetic variations in statin metabolism and response; (3) differences in healthcare systems and medication adherence; and (4) variability in HCC surveillance intensity and diagnostic practices. The extremely high heterogeneity in Western populations (I^2=92.5%) is particularly concerning and substantially limits the interpretability and generalizability of the pooled Western estimate. In this context, the pooled Western HR (0.70, 95% CI 0.54–0.89) should be regarded as an exploratory estimate only.

4.2. Sources of heterogeneity

Beyond geographic differences, several additional sources of heterogeneity across included reviews deserve consideration. First, disease etiology: the included reviews encompass populations with viral hepatitis B and C, MASLD, alcohol-related liver disease, and mixed etiologies, which differ substantially in their pathophysiology, baseline inflammatory milieu, and pharmacogenomic response to statin therapy. Second, statin type and dose: the majority of observational evidence does not differentiate between statin molecules or dose regimens, while RCT evidence has focused predominantly on simvastatin. Whether the observed associations are class effects or molecule-specific remains unknown. Third, disease severity: cirrhotic and non-cirrhotic populations, as well as compensated and decompensated patients, are frequently pooled within individual reviews. As discussed above, the benefit-risk profile of statins may differ substantially across these groups. Fourth, follow-up duration: shorter studies may miss late-onset benefits (e.g. HCC prevention) while longer studies may be more affected by competing risks, particularly in advanced disease. These sources of heterogeneity preclude straightforward generalization of the pooled estimates to individual patient subgroups and should inform the design of future trials. Likewise, the substantial heterogeneity observed for mortality may reflect differences in follow-up duration, competing risks, and variations in cause-of-death ascertainment across studies. Nevertheless, even with relatively weaker evidence in Western populations, the high prevalence of MASLD—conditions closely linked to elevated cardiovascular risk—supports the continued consideration of statins in this setting when cardiovascular indications are present.

4.3. Safety: compensated versus decompensated cirrhosis

Importantly, hepatotoxicity rates are comparable to those in non-cirrhotic populations and severe events occur in less than 1% of patients, indicating that statins remain safe in compensated cirrhosis. In decompensated cirrhosis, the evidence base for both efficacy and safety is substantially more limited. The LIVERHOPE-2 trial [43], which examined simvastatin plus rifaximin in decompensated patients, did not demonstrate a reduction in decompensation or mortality, and the LIVERHOPE-SAFETY trial documented dose-related adverse events including muscle toxicity. Dose-dependent risks — particularly associated with simvastatin 40 mg — have also been highlighted in RCT-based meta-analyses[23]. These data collectively support restricting statin use in decompensated cirrhosis to carefully selected patients at low risk of adverse events, with preference for low-dose regimens, pending definitive trial evidence. In compensated cirrhosis, where the safety profile appears acceptable and the potential cardiovascular and hepato-

protective benefits are plausible, the benefit-risk balance is more favorable.

Our findings also highlight persisting uncertainties. Most of the observed associations derive from observational studies, and truly definitive evidence requires well-designed randomized controlled trials. The ongoing SACRED trial [42], evaluating simvastatin in 2,400 patients with high-risk compensated cirrhosis, is therefore crucial to determine whether the magnitude of association suggested by observational data is reproducible under randomized conditions. Evidence in decompensated cirrhosis remains particularly limited. The LIVERHOPE-2 trial [43], which examined simvastatin plus rifaximin in decompensated cirrhosis, did not demonstrate a reduction in decompensation or mortality, in contrast to earlier observational signals. However, important methodological limitations—including lack of baseline lipid data, unclear achievement of lipid-lowering targets, and uncertainties regarding statin dosing—temper the interpretation of these negative findings and do not definitively rule out benefit in carefully selected patients.

Beyond geographical heterogeneity, additional limitations must be acknowledged. Reliance on aggregate data from systematic reviews rather than individual patient data limits our ability to explore patient-level predictors of treatment response or to conduct network meta-analysis. The evidence based is largely derived from observational studies, raising the possibility of residual confounding; specifically, immortal time bias, confounding by indication, and healthy user bias are well-documented sources of overestimation in pharmacoepidemiologic studies and are likely to have affected the primary studies included across reviews. However, the consistency of findings across multiple independent research groups provides some reassurance. Formal stratification by cirrhosis severity (compensated versus decompensated) was not feasible from aggregate data, as most included reviews did not consistently report results by disease stage; this represents a meaningful limitation, as the benefit-risk profile is likely to differ substantially between these populations. Finally, although our hierarchical exclusion strategy was necessary to minimize dataset overlap, it may have inadvertently omitted relevant evidence, particularly from smaller or regional studies. Nevertheless, this umbrella review offers methodological advance in hepatology evidence synthesis through several key strengths. First, our rigorous application of the corrected covered area methodology substantially reduced the risk of data duplication, an often-overlooked critical issue in systematic reviews that can artificially inflate effect estimates. Second, the use of AMSTAR-2 for comprehensive quality assessment ensures that our conclusions rest on methodologically robust and transparently evaluated reviews. Third, extensive scope of our analysis, incorporating data from several million participants across 34 countries, provides unprecedented power to detect true treatment effects and explore sources of heterogeneity. Fourth, the explicit structured comparison of observational and RCT-derived evidence for decompensation and mortality outcomes represents an important addition to prior syntheses in this field.

4.4. Clinical implications

The findings of this umbrella review have several pragmatic clinical implications. First, statins should not be withheld from patients with CLD — including compensated cirrhosis — when a cardiovascular indication exists; the available evidence does not support hepatotoxicity concerns in this population, and observational associations with hepatological benefit are consistent. Second, the current evidence does not support initiating statin therapy for primary hepatological indications (HCC prevention or decompensation reduction) outside the context of clinical trials, given the predominantly observational nature of the supporting evidence and the lack of RCT confirmation. Third, in decompensated cirrhosis, caution is warranted: statins should be used at the lowest effective dose, with close monitoring, and high-dose regimens (particularly simvastatin ≥40 mg) should be avoided. Fourth, geographic differences in the magnitude of association — and the predominantly HBV-driven evidence from Asian cohorts — limit the direct transferability of effect size estimates to Western populations where MASLD and alcohol-related liver disease predominate.

5. Conclusions

This umbrella review demonstrates that statin use is consistently associated with reduced HCC risk and hepatic decompensation in patients with CLD, with particularly strong associations in Asian populations. However, these findings derive predominantly from observational evidence and are susceptible to confounding by indication, healthy user bias, and immortal time bias; causal inference therefore remains premature. Available RCT evidence does not consistently confirm a benefit for decompensation or mortality endpoints. The coherence of observational associations across multiple independent research groups, combined with biological plausibility and an acceptable safety profile in compensated cirrhosis, supports the continued use of statins in patients with CLD where cardiovascular indications are present, with potential additive hepatoprotective benefit. Safety data in decompensated cirrhosis are limited, and high-dose regimens should be avoided in this population. Our results underscore the urgent need for adequately powered randomized trials — particularly the ongoing SACRED trial — mechanistic studies, and dedicated investigations in decompensated cirrhosis to clarify the boundaries of safety and efficacy in this high-risk population.

Author contributions

FC, MV, MZ, AM, VDM and LAN: study concept and design, data acquisition, analysis and interpretation, manuscript drafting; DS: critical revision for important intellectual content; RL and AD: study supervision and final approval. All authors approved the final version of the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information file.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

thanks to PNRR-MCNT2-2023-12378295 IMMUNOMIC.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2026.05.010.

References

[1] GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5(3):245–66 MarEpub 2020 Jan 22. PMID: 31981519; PMCID: PMC7026710. doi:10.1016/S2468-1253(19)30349-8.

[2] Arroyo V, Moreau R, Kamath PS, Jalan R, Ginès P, Nevens F, Fernández J, To U, García-Tsao G, Schnabl B. Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primers 2016;2:16041 Jun 9PMID: 27277335. doi:10.1038/nrdp.2016.41.

[3] Bader T. Yes! statins can be given to liver patients. J Hepatol 2012;56(2):305–7 PMID: 21963520. doi:10.1016/j.jhep.2011.08.016.

[4] Pose E, Trebicka J, Mookerjee RP, Angeli P, Statins Ginès P. Old drugs as new therapy for liver diseases? J Hepatol 2019;70(1):194–202 JanEpub 2018 Aug 1. PMID: 30075229. doi:10.1016/j.jhep.2018.07.019.

[5] Dolivo DM, Reed CR, Gargiulo KA, Rodrigues AE, Galiano RD, Mustoe TA, Hong SJ. Anti-fibrotic effects of statin drugs: a review of evidence and mechanisms. Biochem Pharmacol 2023;214:115644 AugEpub 2023 Jun 13. PMID: 37321414. doi:10.1016/j.bcp.2023.115644.

[6] Arnaud C, Braunersreuther V, Mach F. Toward immunomodulatory and anti-inflammatory properties of statins. Trends Cardiovasc Med 2005;15(6):202–6 AugPMID: 16182129. doi:10.1016/j.tcm.2005.07.002.

[7] Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature 1990;343(6257):425–30 Feb 1PMID: 1967820. doi:10.1038/343425a0.

[8] Trebicka J, Hennenberg M, Laleman W, Shelest N, Biecker E, Schepke M, Nevens F, Sauerbruch T, Heller J. Atorvastatin lowers portal pressure in cirrhotic rats by inhibition of RhoA/rho-kinase and activation of endothelial nitric oxide synthase. Hepatology 2007;46(1):242–53 JulPMID: 17596891. doi:10.1002/hep.21673.

[9] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359(21):2195–207 Nov 20Epub 2008 Nov 9. PMID: 18997196. doi:10.1056/NEJMoa0807646.

[10] Rombouts K, Kisanga E, Hellemans K, Wielant A, Schuppan D, Geerts A. Effect of HMG-CoA reductase inhibitors on proliferation and protein synthesis by rat hepatic stellate cells. J Hepatol 2003;38(5):564–72 MayPMID: 12713866. doi:10.1016/s0168-8278(03)00051-5.

[11] Kamal S, Khan MA, Seth A, Cholankeril G, Gupta D, Singh U, Kamal F, Howden CW, Stave C, Nair S, Satapathy SK, Ahmed A. Beneficial effects of statins on the rates of hepatic fibrosis, hepatic decompensation, and mortality in chronic liver disease: a systematic review and meta-analysis. Am J Gastroenterol 2017;112(10):1495–505 OctEpub 2017 Jun 6. PMID: 28585556. doi:10.1038/ajg.2017.170.

[12] Wong YJ, Qiu TY, Ng GK, Zheng Q, Teo EK. Efficacy and safety of Statin for hepatocellular carcinoma prevention among chronic liver disease patients: a systematic review and meta-analysis. J Clin Gastroenterol 2021;55(7):615–23 Aug 1PMID: 33606427. doi:10.1097/MCG.0000000000001478.

[13] Li Z, Li Y, Li X, Zhang L, Zhao N, Du H, Zhou B, Ye Y. Statins in Hepatitis B or C patients is associated with reduced hepatocellular carcinoma risk: a systematic review and meta-analysis. Turk J Gastroenterol 2022;33(2):136–44 FebPMID: 35115293; PMCID: PMC9128600. doi:10.5152/tjg.2020.19656.

[14] Björkhem-Bergman L, Backheden M, Söderberg Löfdal K. Statin treatment reduces the risk of hepatocellular carcinoma but not colon cancer-results from a nationwide case-control study in Sweden. Pharmacoepidemiol Drug Saf 2014;23(10):1101–6 OctEpub 2014 Jul 29. PMID: 25074765. doi:10.1002/pds.3685.

[15] Zhang J, Fu S, Liu D, Wang Y, Tan Y. Statin can reduce the risk of hepatocellular carcinoma among patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2023;35(4):353–8 Apr 1Epub 2023 Jan 31. PMID: 36719824. doi:10.1097/MEG.0000000000002517.

[16] Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol 2014;67(4):368–75 AprPMID: 24581293. doi:10.1016/j.jclinepi.2013.11.007.

[17] Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q 2016;94(3):485–514 SepPMID: 27620683; PMCID: PMC5020151. doi:10.1111/1468-0009.12210.

[18] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008 Sep 21PMID: 28935701; PMCID: PMC5833365. doi:10.1136/bmj.j4008.

[19] Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol 2014;67(4):368–75 AprPMID: 24581293. doi:10.1016/j.jclinepi.2013.11.007.

[20] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60 Sep 6PMID: 12958120; PMCID: PMC192859. doi:10.1136/bmj.327.7414.557.

[21] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34 Sep 13PMID: 9310563; PMCID: PMC2127453. doi:10.1136/bmj.315.7109.629.

[22] Ayada I, van Kleef LA, Zhang H, Liu K, Li P, Abozaid YJ, Lavrijsen M, Janssen HLA, van der Laan LJW, Ghanbari M, Peppelenbosch MP, Zheng MH, de Knegt RJ, Pan Q. Dissecting the multifaceted impact of statin use on fatty liver disease: a multidimensional study. EBioMedicine 2023;87:104392 JanEpub 2022 Dec 8. PMID: 36502575; PMCID: PMC9758527. doi:10.1016/j.ebiom.2022.104392.

[23] Abdulrazzak E, Fakhoury B, Jaan A, Ebrahim M, Alabdul Razzak I, Shehadah A, Sierra L, Abosheaishaa H, Tapper EB, Trivedi HD. Statin therapy and portal pressure reduction in cirrhosis: A systematic review and meta-analysis. Liver Int 2025;45(10):e70326 OctPMID: 40891266. doi:10.1111/liv.70326.

[24] Boutari C, Pappas PD, Anastasilakis D, Mantzoros CS. Statins' efficacy in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Clin Nutr 2022;41(10):2195–206 OctEpub 2022 Aug 8. PMID: 36081293. doi:10.1016/j.clnu.2022.08.001.

[25] Fatima K, Moeed A, Waqar E, Atif AR, Kamran A, Rizvi H, Suri NF, Haider H, Shuja SH, Khalid M, Minhas AMK. Efficacy of statins in treatment and development of non-alcoholic fatty liver disease and steatohepatitis: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2022;46(4):101816 AprEpub 2021 Oct 2. PMID: 34607067. doi:10.1016/j.clinre.2021.101816.

[26] Gu Y, Yang X, Liang H, Li D. Comprehensive evaluation of effects and safety of statin on the progression of liver cirrhosis: a systematic review and meta-analysis. BMC Gastroenterol 2019;19(1):231 Dec 30PMID: 31888534; PMCID: PMC6938024. doi:10.1186/s12876-019-1147-1.

[27] Kim RG, Loomba R, Prokop LJ, Singh S. Statin use and risk of cirrhosis and related complications in patients with chronic liver diseases: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2017;15(10):1521–1530.e8 Octe8Epub 2017 May 4. PMID: 28479502; PMCID: PMC5605397. doi:10.1016/j.cgh.2017.04.039.

[28] Ma X, Sun D, Li C, Ying J, Yan Y. Statin use and virus-related cirrhosis: A systemic review and meta-analysis. Clin Res Hepatol Gastroenterol 2017;41(5):533–42 OctEpub 2017 Aug 31. PMID: 28866088. doi:10.1016/j.clinre.2017.07.004.

[29] Sung S, Al-Karaghouli M, Kalainy S, Cabrera Garcia L, Abraldes JG. A systematic review on pharmacokinetics, cardiovascular outcomes and safety profiles of statins in cirrhosis. BMC Gastroenterol 2021;21(1):120 Mar 16PMID: 33726685; PMCID: PMC7967963. doi:10.1186/s12876-021-01704-w.

[30] Vahedian-Azimi A, Shojaie S, Banach M, Heidari F, Cicero AFG, Khoshfetrat M, Jamialahmadi T, Sahebkar A. Statin therapy in chronic viral hepatitis: a systematic review and meta-analysis of nine studies with 195,602 participants. Ann Med 2021;53(1):1228–43 DecPMID: 34296976; PMCID: PMC8317925. doi:10.1080/07853890.2021.1956686.

[31] Wang Y, Wang W, Wang M, Shi J, Jia X, Dang S. A meta-analysis of statin use and risk of hepatocellular carcinoma. Can J Gastroenterol Hepatol 2022;2022:1–15 Mar 20PMID: 35356132; PMCID: PMC8958112. doi:10.1155/2022/5389044.

[32] Zhang H, Zhang Q, Li S, Xie B. Simvastatin is efficacious in treating cirrhosis: A meta-analysis. J Clin Gastroenterol 2022;56(8):e303–12 Sep 1Epub 2022 Jul 14. PMID: 35830548. doi:10.1097/MCG.0000000000001732.

[33] Zeng RW, Yong JN, Tan DJH, Fu CE, Lim WH, Xiao J, Chan KE, Tan C, Goh XL, Chee D, Syn N, Tan EX, Muthiah MD, Ng CH, Tamaki N, Lee SW, Kim BK, Nguyen MH, Loomba R, Huang DQ. Meta-analysis: chemoprevention of hepatocellular carcinoma with statins, aspirin and metformin. Aliment Pharmacol Ther 2023;57(6):600–9 MarEpub 2023 Jan 10. PMID: 36625733; PMCID: PMC10792521. doi:10.1111/apt.17371.

[34] Zheng Yi-Xiang, Zhou Peng-Cheng, Zhou Rong-Rong, Fan Xue-Gong. The benefit of statins in chronic hepatitis C patients: a systematic review and meta-analysis. Eur J Gastroenterol Hepatology 2017;29(7):759–66 July|. doi:10.1097/MEG.0000000000000867.

[35] Ramos-Tovar E, Muriel P. Molecular mechanisms that link oxidative stress, inflammation, and fibrosis in the liver. Antioxidants (Basel). 2020 Dec 15;9(12):1279. doi: 10.3390/antiox9121279. PMID: 33333846; PMCID: PMC7765317.

[36] Garcia-Ruiz C, Fernandez-Checa JC. Mitochondrial glutathione: hepatocellular survival-death switch. J Gastroenterol Hepatol 2006;21 Oct;21 Suppl 3:S3-6PMID: 16958667. doi:10.1111/j.1440-1746.2006.04570.x.

[37] Mo H, Elson CE. Studies of the isoprenoid-mediated inhibition of mevalonate synthesis applied to cancer chemotherapy and chemoprevention. Exp Biol Med (Maywood) 2004;229(7):567–85 JulPMID: 15229351. doi:10.1177/153537020422900701.

[38] Berndt N, Hamilton AD, Sebti SM. Targeting protein prenylation for cancer therapy. Nat Rev Cancer 2011;11(11):775–91 Oct 24PMID: 22020205; PMCID: PMC4037130. doi:10.1038/nrc3151.

[39] Liang W, Shi J, Xia H, Wei X. A novel ruthenium-fluvastatin complex down-regulates SNCG expression to modulate breast carcinoma cell proliferation and apoptosis via activating the PI3K/akt/mTOR/VEGF/MMP9 pathway. Oxid Med Cell Longev 2021;2021:5537737 Jun 7PMID: 34221232; PMCID: PMC8221895. doi:10.1155/2021/5537737.

[40] Dahan J, Nouët Y, Jouvion G, Levillayer F, Adib-Conquy M, Cassard-Doulcier AM, Tebbi A, Blanc F, Remy L, Chen J, Cairo S, Werts C, Si-Tahar M, Tordjmann T, Buendia MA, Wei Y. LIM-only protein FHL2 activates NF-κb signaling in the control of liver regeneration and hepatocarcinogenesis. Mol Cell Biol 2013;33(16):3299–308 AugEpub 2013 Jun 17. PMID: 23775124; PMCID: PMC3753919. doi:10.1128/MCB.00105-13.

[41] Jamialahmadi T, Reiner Z, Riahi MM, Emami SA, Tayarani-Najaran Z, Salehabadi S, Kesharwani P, Al-Rasadi K, Sahebkar A. Statins and portal hypertension: A systematic review and meta-analysis of randomized controlled

trials. Curr Med Chem 2025;32(7):1323–32 PMID: 37723637. doi:10.2174/0929867331666230918114451.

[42] Kaplan DE, Mehta R, Garcia-Tsao G, Albrecht J, Aytaman A, Baffy G, Bajaj J, Hernaez R, Hunt K, Ioannou G, Johnson K, Kanwal F, Lee TH, Monto A, Pandya P, Schaubel D, Taddei TH. SACRED: effect of simvastatin on hepatic decompensation and death in subjects with high-risk compensated cirrhosis: statins and cirrhosis: reducing events of decompensation. Contemp Clin Trials 2021;104:106367 MayEpub 2021 Mar 24. PMID: 33771685; PMCID: PMC8422958.. doi:10.1016/j.cct.2021.106367.

[43] Pose E, Napoleone L, Amin A, Campion D, Jimenez C, Piano S, Roux O, Uschner FE, de Wit K, Zaccherini G, Alessandria C, Angeli P, Bernardi M, Beuers U, Caraceni P, Durand F, Mookerjee RP, Trebicka J, Vargas V, Andrade RJ, Carol M, Pich J, Ferrero J, Domenech G, Llopis M, Torres F, Kamath PS, Abraldes JG, Solà E, Ginès P. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Gastroenterol Hepatol 2020;5(1):31–41 JanEpub 2019 Oct 10. PMID: 31607677. doi:10.1016/S2468-1253(19)30320-6.