Association between statin exposure and short-term mortality in patients with high-grade acute-on-chronic liver failure

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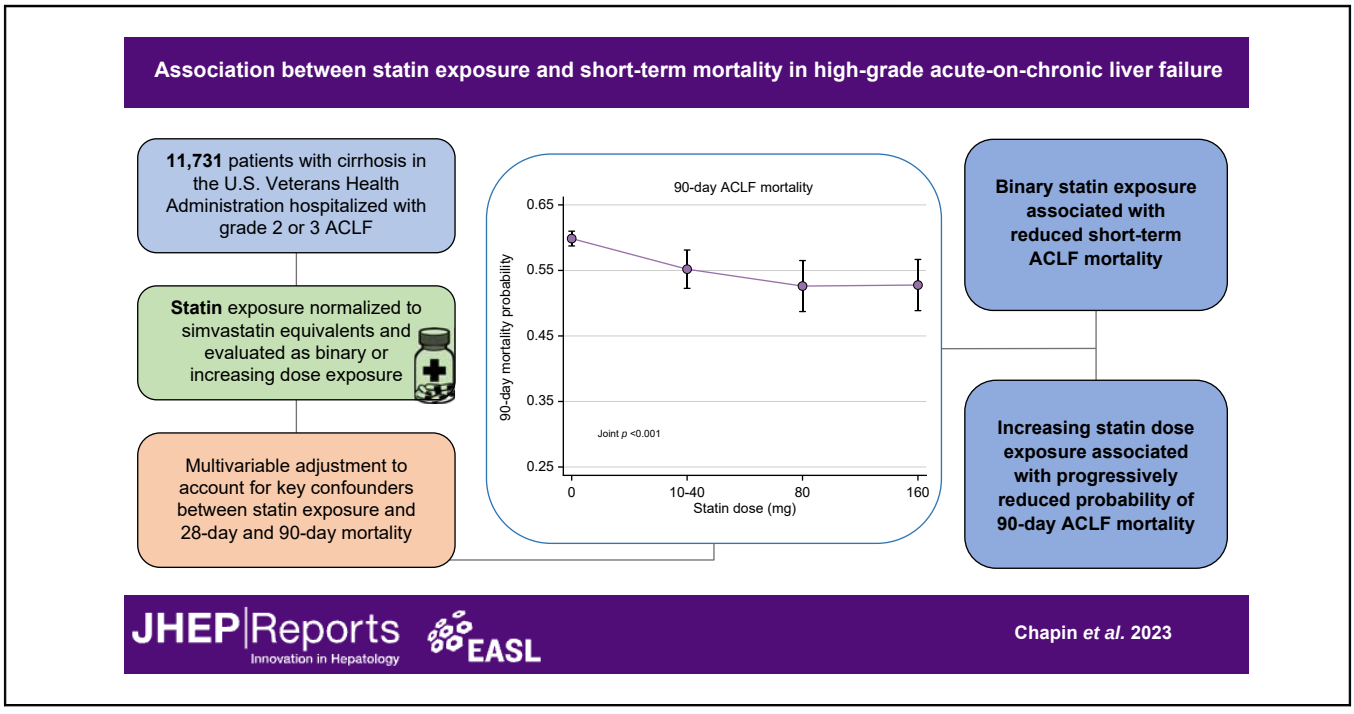
Graphical abstract



Highlights

- Statin exposure in patients with cirrhosis and ACLF is associated with reduced short-term mortality.
- Increasing statin dose exposure is associated with further reduction in 90-day mortality.
- A greater degree of mortality reduction with statin exposure was observed in patients with prior compensated cirrhosis.

Impact and Implications

Statins have been identified as a class of medications with potential beneficial effects for patients with cirrhosis. In this large, retrospective cohort study of patients with cirrhosis who seek care at the Veterans Health Administration, statin use was associated with a decrease in short term (28-day and 90-day) mortality as a result of acute-on-chronic liver failure. Future prospective studies are needed to further clarify the relative safety and efficacy of statin therapy in reducing morbidity and mortality associated with acute-on-chronic liver failure in patients with cirrhosis.

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Research article

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Association between statin exposure and short-term mortality in patients with high-grade acute-on-chronic liver failure

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Background & Aims: Acute-on-chronic liver failure (ACLF) carries a high short-term mortality for patients with cirrhosis. Prior literature suggests that statin exposure may reduce the likelihood of ACLF events. However, it is unclear if statin exposure is associated with ACLF-related mortality. This study sought to determine the association between statin use and short-term mortality among patients hospitalised with ACLF.

Methods: This was a retrospective cohort study of Veterans Health Administration (VHA) patients diagnosed with cirrhosis between 2008 and 2021 and hospitalised with high-grade (2 or 3) ACLF. Patients were stratified into those with and without continuous statin exposure for at least 90 days prior to hospitalisation. Multivariable logistic regression models were created to determine the adjusted association between statin exposure and 28-day and 90-day mortality. Categorical statin dose exposure, converted to simvastatin equivalents, was also explored.

Results: A total of 11,731 patients with cirrhosis hospitalised with Grade 2 or 3 ACLF were included in the analytic cohort, 26% of whom had statin exposure. In adjusted logistic regression models, statin use was associated with 18% lower odds of ACLF-related 28-day mortality (odds ratio [OR] 0.82, 95% CI 0.73–0.93, $p = 0.001$) and 24% lower odds of 90-day mortality (OR 0.76, 95% CI 0.68–0.86, $p < 0.001$). Increasing statin dose exposure was also associated with further reductions in 90-day mortality (*e.g.* OR 0.81, 95% CI 0.70–0.93 for 10–40 mg *vs.* 0 mg and OR 0.72, 95% CI 0.60–0.87 for 80 mg *vs.* 0 mg, $p < 0.001$).

Conclusions: In this large, retrospective cohort study, statin exposure before high-grade ACLF hospitalisation was associated with reduced odds of 28-day and 90-day mortality in patients with cirrhosis. A statin dose-dependent reduction in 90-day ACLF-related mortality was also observed.

Impact and Implications: Statins have been identified as a class of medications with potential beneficial effects for patients with cirrhosis. In this large, retrospective cohort study of patients with cirrhosis who seek care at the Veterans Health Administration, statin use was associated with a decrease in short term (28-day and 90-day) mortality as a result of acute-on-chronic liver failure. Future prospective studies are needed to further clarify the relative safety and efficacy of statin therapy in reducing morbidity and mortality associated with acute-on-chronic liver failure in patients with cirrhosis.

Introduction

Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome where acute decompensation events in patients with chronic liver disease prompt a hyperinflammatory state leading to organ failure (OF).[1] ACLF carries a high short-term mortality, with a 90-day mortality rate surpassing 50%.[1,2]

Given the high risk of death associated with ACLF events, there is great interest in identifying potential factors that may prevent the development of ACLF or improve the prognosis of ACLF. The statin class of medications is one potential exposure that may plausibly improve ACLF-related outcomes. Along with lipid lowering effects, statins have recognised pleiotropic effects including anti-inflammatory, anti-oxidant, antifibrotic, and vasoactive properties, which may be beneficial for patients with chronic liver disease.[3–5] In addition to several observational studies showing an association between statin therapy and the reduced risk of hepatic decompensation and death in patients with cirrhosis, recent work within our group demonstrated an association between statin use and reduced development of ACLF in a large, Veterans Affairs cohort.[4,6–8] However, the potential impact of statin exposure on short-term outcomes in patients who have already developed ACLF remains unexplored. This is an important area of research needed to provide a more comprehensive understanding of the potential role of statins in patients with advanced liver disease and ACLF.

Keywords: Acute-on-chronic liver failure; Veterans health administration; Statins; Short-term mortality; Infection.

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To address this knowledge gap, we used a large dataset of patients with established cirrhosis to explore the association between statin exposure and short-term mortality (28 days and 90 days) among patients hospitalised with high-grade ACLF.

Patients and methods

Study design and cohort creation

This was a retrospective cohort study utilising data from the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) cohort, the derivation of which has been previously described.[9] The VOCAL cohort includes longitudinal data from approximately 130,000 patients with cirrhosis, age 18 yr or older, who received care in the Veteran Health Administration (VHA) between January 1, 2008 and March 31, 2021, and has been used for numerous natural history studies of patients with cirrhosis.[10–14] A validated algorithm of one inpatient or two outpatient International Classification of Diseases (ICD)-9/10 codes for cirrhosis (571.2, 571.5, K74.6x, K70.3x) was utilised to classify cirrhosis.[15]

Identification of patients with cirrhosis hospitalised with a high-grade ACLF event was accomplished utilising the European Association for the Study of the Liver–Chronic Liver Failure (EASL–CLIF) criteria;[1] we focused on this definition for consistency with our prior work on statin exposure and ACLF development.[8] Classification of ACLF within the VHA dataset has been previously described.[8,16–18] To summarise, patients with cirrhosis who were hospitalised were identified with data regarding acute decompensations (ADs) including infection, gastrointestinal bleed, ascites, or hepatic encephalopathy ascertained via ICD-9/10 codes, current procedural terminology (CPT) codes, and medication administration information. OFs that occurred with 28 days of hospitalisation, including kidney, liver, coagulation, respiratory, brain, and circulatory failures were classified using laboratory, medication administration data, and administrative coding. ACLF severity grades were categorised from 0 (no ACLF) to 3 (severe ACLF) with high-grade ACLF considered to be a Grade 2 or 3. Details of AD and OF classification are provided in Tables S1–S5, and have been previously published in the VOCAL cohort.[8,16,17,19] In this study, we included patients aged 18 yr or older with cirrhosis who experienced a first hospitalisation with high-grade ACLF (2 or 3). We excluded patients who received liver transplantation before hospitalisation.

Exposure variables

Information regarding patient demographics (age, sex, race), liver disease (aetiology, decompensated status), comorbidities (coronary artery disease, heart failure, atrial fibrillation, diabetes mellitus), other health information (BMI, smoking status), and hospital day of admission data (laboratory, vital signs) were collected following prior methods.[9,16] The model for end-stage liver disease-sodium (MELD-Na) was calculated from laboratory data on admission. We also obtained pre-morbid (*i.e.* most recent before hospitalisation) MELD-Na and Child–Turcotte–Pugh class; the latter was determined using a validated VHA algorithm.[9]

All statin prescriptions from the time of cirrhosis diagnosis through maximum cohort follow-up were obtained for patients by querying VHA pharmacy dispensation data. Patients were considered exposed to statins if they had continuous pharmacy fills covering the 90 days before hospitalisation. Statin doses were converted to simvastatin equivalents with categories including 0 mg (*i.e.* no statin exposure), 10–40 mg, 80 mg, or 160 mg, based on prior methods.[7,8]

Outcome variable

The primary outcome was short-term mortality at 28 days or 90 days from hospitalisation. Mortality data in the VHA are highly accurate and were obtained from the Vital Status File.[20]

Primary statistical analysis

Descriptive statistics for the study cohort were reported as frequencies and percentages for categorical variables and as medians and IQRs for continuous variables. The study cohort was stratified into those with no statin exposure and those with any statin exposure (as defined above) before hospital admission. Statistical comparisons were performed between these two groups using Wilcoxon rank-sum and chi-square tests for continuous and categorical data, respectively. Comparisons between statin exposed and unexposed were also performed for ACLF-related data including ADs, OFs, and short-term mortality.

Multivariable logistic regression models were utilised to determine the association between statin exposure and 28-day and 90-day mortality among patients hospitalised with high-grade ACLF. An *a priori* modelling approach based on clinical reasoning and prior literature[17,18,21,22] was used to select variables for adjustment in final models. These variables included age, smoking status, BMI, aetiology of liver disease, diabetes, coronary artery disease (CAD), prior decompensated cirrhosis status, MELD-Na at time of hospital admission, and albumin at time of hospital admission. Linearity of continuous variables with respect to the outcome in logistic regression models was evaluated and confirmed using locally weighted scatterplot smoothing (LOWESS) plots. Four final models were fit to assess 28-day and 90-day mortality with (1) binary statin exposure (statin exposed *vs.* non-exposed) and (2) categorical statin dose exposure (0 mg, 10–40 mg, 80 mg, 160 mg) as primary exposures. Odds ratios (ORs) with 95% CIs were presented. Marginal probabilities of the outcome were plotted for categorical statin dose exposure models. The threshold for statistical significance was set to alpha = 0.05. Finally, in a sensitivity analysis to address the possibility of healthy user bias, we additionally adjusted for pre-morbid CTP class and MELD-Na in primary models.

Inverse probability treatment weighting sensitivity analysis

Given the possibility of residual confounding in the *a priori* models above, we performed a sensitivity analysis with broad inclusion of variables in an inverse probability treatment weighting (IPTW) approach. We constructed a propensity score (PS) for statin exposure using the following variables: age, sex, race, BMI, aetiology of liver disease, smoking history, diabetes, atrial fibrillation, CAD, heart failure, prior cirrhosis decompensation, pre-hospitalisation MELD-Na, pre-hospitalisation CTP class, admission MELD-Na, admission albumin, and admission platelet count. Inverse probability weights were computed as 1/PS for statin-exposed patients and as 1/(1-PS) for statin non-exposed patients. Standardised mean differences (SMDs) for the unweighted and IPTW pseudocohort were then plotted, where SMDs between -0.1 and 0.1 were regarded to represent excellent balance, consistent with best practice recommendations.[23] IPTW-adjusted logistic regression models were then run for 28-day and 90-day mortality primary outcomes, with additional covariate adjustment for age, which was not sufficiently balanced through the IPTW procedure.

Exploratory analyses

To further explore the association between statin exposure and ACLF-related mortality, additional exploratory analyses were conducted. To approximate the potential anti-inflammatory effect of statin medications, Wilcoxon rank-sum tests were performed between statin exposed and unexposed groups to evaluate differences in maximum white blood cell (WBC) count in the first 28 days of hospital admission, stratified by the presence or absence of infection. To evaluate potential differences in the association between statin exposure and short-term mortality in previously decompensated *vs.* compensated patients with cirrhosis, we evaluated an interaction term between categorical statin dose exposure and prior decompensation status in adjusted models.

Other considerations

This study received Institutional Review Board approval from the Michael J. Crescenz Philadelphia Veterans Affairs Medical Center. All analyses were performed using STATA/BE 17.0 (College Station, TX, USA; see also Supplementary CTAT Table).

Results

Cohort characteristics

A total 12,253 patients with cirrhosis and high-grade ACLF hospitalisations were identified in the VOCAL cohort, of whom 522 were excluded for prior liver transplantation. The analytic cohort thus comprised 11,731 patients. This study cohort was primarily male (98.4% *vs.* 97%) and white (58% *vs.* 54.5%) in statin-exposed and statin-unexposed groups, respectively. Patients with statin exposure (n = 3,017, 25.7%) were older (median 67 *vs.* 62 yr, p <0.001), had higher BMI (30.5 *vs.* 28.3, p <0.001), and more medical comorbidities as compared with unexposed patients (Table 1). The statin-unexposed group had a higher percentage of patients with decompensated cirrhosis at baseline (70.9% *vs.* 56.8% in statin-exposed patients, p <0.001). MELD-Na at time of hospital admission was higher in the statin-unexposed group (29, IQR 23–34) *vs.* the statin-exposed group (27, IQR 22–32, p <0.001).

In terms of ACLF acute decompensation events, the statin-exposed group demonstrated a higher burden of infection (64.5% *vs.* 59.6% in the statin-unexposed group, p <0.001; Table 2), whereas the statin-unexposed group had higher rates of hepatic encephalopathy (39.2% *vs.* 21.6% in statin-exposed individuals, p <0.001), ascites (41.7% *vs.* 33.1% in statin-exposed individuals, p <0.001), and gastrointestinal bleeding (27.3% *vs.* 24.7% in statin-exposed individuals, p = 0.006). The statin-unexposed group had higher rates of liver OF (28.8% *vs.* 9.4% in the statin-exposed group, p <0.001) and brain OF (39.2% *vs.* 21.6% in statin-exposed patients, p <0.001) whereas the statin-exposed group had rates of circulatory OF (48.4% *vs.* 43.1% in statin-unexposed individuals, p <0.001) and kidney OF (85.4% *vs.* 73.1% in statin-unexposed individuals, p <0.001).

ACLF-related short-term mortality by binary statin exposure

Patients unexposed to statins had higher crude 28-day and 90-day mortality compared with statin-exposed patients (44.6% *vs.* 31.8% 28-day mortality, p <0.001 and 61.2% *vs.* 46.8% 90-day mortality, p <0.001, respectively; Table 2). In unadjusted logistic regression modelling, patients with statin exposure had a 42% lower odds of 28-day mortality relative to statin-unexposed patients (OR 0.58, 95% CI 0.53–0.63, p <0.001) and a 44% lower odds of 90-day mortality (OR 0.56, 95% CI 0.51–0.61, p <0.001). When controlling for potential confounders utilising multivariable logistic regression, statin use was associated with a 18% reduction in ACLF-related 28-day mortality (OR 0.82, 95% CI 0.73–0.93, p = 0.001) and a 24% reduction in ACLF-related 90-day mortality (OR 0.76, 95% CI 0.68–0.86, p <0.001; Table 3). In a sensitivity analysis additionally controlling for pre-morbid MELD-Na and CTP class, the effect size for statin exposure was similar at 28 days (OR 0.82, 95% CI 0.73–0.92, p = 0.001) and 90 days (OR 0.77, 95% CI 0.69–0.87, p <0.001) as compared with primary models. Finally, in IPTW sensitivity analyses, excellent covariate balance was achieved, with the exception of age which had an SMD slightly greater than 0.1 (Fig. S1). In IPTW-adjusted logistic regression models additionally adjusted for age, results were generally similar to the primary analyses; statin exposure was significantly associated with reduced odds of 28-day mortality (OR 0.91, 95% CI 0.86–0.97, p = 0.002) and 90-day mortality (OR 0.89, 95% CI 0.84–0.94, p <0.001).

ACLF-related short-term mortality by categorical statin dose exposure

In categorical statin dose models, there was a significant association between statin dose and ACLF-related mortality at both 28 and 90 days. For example, in the 90-day mortality model, 10–40 mg was associated with a 19% reduced odds of mortality *vs.* 0 mg (OR 0.81, 95% CI 0.70–0.93) and 80 mg or 160 mg were associated with 27–28% reduced odds of mortality (OR 0.72, 95% 0.60–0.87 for 80 mg and OR 0.73, 95% CI 0.60–0.87 for 160 mg; Table 4). In the 28-day mortality model, the relative odds of mortality decreased from 10–40 mg to 80 mg, but increased with 160 mg dose exposure, relative to 0 mg. These relationships are summarised in Fig. 1A and B.

Exploratory analyses

In those without infection, statin-exposed patients had significantly lower maximum WBC count *vs.* statin-unexposed patients (median 9.5 *vs.* 10.4, p <0.001; Fig. 2). For those with infection, the statin-exposed group also demonstrated lower maximum WBC count *vs.* statin-unexposed patients (median 14.6 *vs.* 15.7, p <0.001). Finally, in the 90-day adjusted mortality model there was a significant interaction between statin dose and prior decompensation; a greater degree of mortality reduction with increasing statin dose exposure was observed in patients with previously compensated cirrhosis, although this difference was less pronounced in patients receiving maximum statin dose (p = 0.03; Fig. 3B). A similar trend was observed in the 28-day mortality model, however, the interaction term was not statistically significant (p = 0.06; Fig. 3A).

Discussion

In this large, retrospective cohort study, patients exposed to statins before hospitalisation with high-grade ACLF demonstrated lower odds of 28-day and 90-day mortality and this effect was strengthened by exposure to higher doses of statins. Logistic regression modelling was utilised to control for potential confounding variables, including differences in baseline liver health (decompensated cirrhosis status, MELD-Na), further upholding the association of statin use and reduced odds of short-term ACLF-related mortality.

The statin class of medications has become of key interest in the care of patients with cirrhosis, a condition characterised by

Table 1. Baseline cohort characteristics by statin exposure.

Factor	No statin exposure n = 8,714	Any statin exposure n = 3,017	*p* value
Age, year, median (IQR)	62 (56, 66)	67 (62, 72)	<0.001
Male sex	8,450 (97.0%)	2,969 (98.4%)	<0.001
Race			<0.001
White	4,753 (54.5%)	1,749 (58.0%)	
Black	1,702 (19.5%)	637 (21.1%)	
Hispanic	852 (9.8%)	272 (9.0%)	
Asian	112 (1.3%)	52 (1.7%)	
Other	1,295 (14.9%)	307 (10.2%)	
Aetiology			<0.001
HCV	1,016 (11.7%)	270 (8.9%)	
HBV	58 (0.7%)	42 (1.4%)	
EtOH	3,921 (45.0%)	1,159 (38.4%)	
HCV + EtOH	2,601 (29.8%)	471 (15.6%)	
NAFLD	955 (11.0%)	1,021 (33.8%)	
Other	163 (1.9%)	54 (1.8%)	
BMI, median (IQR)	28.26 (24.68, 32.63)	30.47 (26.46, 35.30)	<0.001
Smoking history			<0.001
Never smoker	2,584 (30.3%)	1,140 (38.4%)	
Former smoker	2,875 (33.7%)	1,070 (36.1%)	
Current smoker	3,076 (36.0%)	755 (25.5%)	
Diabetes mellitus	5,246 (60.2%)	2,608 (86.4%)	<0.001
Atrial fibrillation	1,246 (14.3%)	1,273 (42.2%)	<0.001
Coronary artery disease	2,018 (23.2%)	2,000 (66.3%)	<0.001
Heart failure	1,855 (21.3%)	1,833 (60.8%)	<0.001
Decompensated cirrhosis	6,176 (70.9%)	1,713 (56.8%)	<0.001
Ascites	4,600 (52.8%)	1,261 (41.8%)	<0.001
Hepatic encephalopathy	2,436 (28.0%)	532 (17.6%)	<0.001
Pre-morbid CTP class			<0.001
A	3,376 (38.7%)	1,500 (49.7%)	
B	4,561 (52.3%)	1,429 (47.4%)	
C	777 (8.9%)	88 (2.9%)	
Pre-morbid MELD-Na, median (IQR)	18 (12, 23)	18 (12, 23)	0.007
Admission MELD-Na, median (IQR)	29 (23, 34)	27 (22, 32)	<0.001
AST, median (IQR)	74 (44, 137)	46 (28, 92)	<0.001
ALT, median (IQR)	37 (24, 64)	30 (19, 53)	<0.001
Creatinine, median (IQR)	2 (1.2, 3)	2.4 (1.63, 3.68)	<0.001
Total bilirubin, median (IQR)	3.7 (1.7, 9.5)	1.4 (.8, 3)	<0.001
INR, median (IQR)	1.9 (1.46, 2.6)	1.77 (1.33, 2.8)	<0.001
Platelets, median (IQR)	92 (58, 141)	123 (81, 179)	<0.001
Sodium, median (IQR)	133 (128, 136)	134 (131, 137)	<0.001
White blood cell count, median (IQR)	9.2 (6.1, 14.1)	8.655 (6, 12.82)	<0.001
Maximum temperature, median (IQR)	98.3 (97.8, 98.8)	98.3 (97.8, 98.8)	0.61
Minimum temperature, median (IQR)	97.4 (96.7, 97.9)	97.4 (96.8, 97.9)	0.062
Maximum heart rate, median (IQR)	91 (81, 98)	89 (77, 97)	<0.001
Minimum systolic blood pressure, median (IQR)	103 (92, 116)	104 (93, 119)	0.018
Maximum respiratory rate, median (IQR)	20 (18, 22)	20 (18, 22)	0.47

Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the chi-squared test. The threshold for statistical significance was alpha = 5%. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child-Turcotte-Pugh; INR, international normalised ratio; MELD-Na, model for end-stage liver disease-sodium; NAFLD, non-alcoholic fatty liver disease.

impaired hepatic synthetic function and portal hypertension. In addition to their well-known cholesterol lowering effect, statins possess multiple pleiotropic effects that may be advantageous in patients with cirrhosis of multiple aetiologies. These beneficial effects of statins have been described both in animal models of chronic liver disease, where statins have been shown to decrease hepatic inflammation, fibrosis, and portal hypertension,[24,25] as well as in numerous observational studies, where statin use has been associated with decreased risk for hepatic decompensation and death in patients with cirrhosis.[4,6] To date, one randomised controlled trial has demonstrated a significant decrease in the hepatic venous pressure gradient and increased liver perfusion in patients with cirrhosis and portal hypertension taking simvastatin.[26]

Within the context of ACLF, one rat cirrhosis model of ACLF demonstrated the therapeutic effects of simvastatin, reducing hepatic inflammation and portal pressures while also improving overall survival.[27] In addition, work within our group has demonstrated an association with statin exposure and reduced risk for development of high-grade ACLF in patients with cirrhosis; a dose–response effect was also observed in this study.[8] Given these above findings, there is plausibility that statin therapy may reduce both the risk of hepatic decompensation and the development of a hyperinflammatory response in patients with cirrhosis, thus mitigating progression of high-grade ACLF and ACLF-related death.

There are at least two potential mechanisms by which statin therapy may reduce ACLF-related mortality. The anti-

Table 2. Characteristics of acute-on-chronic liver failure decompensations by statin exposure.

Factor	No statin exposure n = 8,714	Any statin exposure n = 3,017	*p* value
Acute decompensation			
Infection	5,197 (59.6%)	1,946 (64.5%)	<0.001
Gastrointestinal bleed	2,378 (27.3%)	746 (24.7%)	0.006
Hepatic Encephalopathy	3,416 (39.2%)	653 (21.6%)	<0.001
Ascites	3,645 (41.8%)	999 (33.1%)	<0.001
Organ failure			
Brain	3,416 (39.2%)	653 (21.6%)	<0.001
Liver	2,506 (28.8%)	285 (9.4%)	<0.001
Coagulation	4,141 (47.5%)	1,384 (45.9%)	0.12
Circulation	3,759 (43.1%)	1,461 (48.4%)	<0.001
Kidney	6,368 (73.1%)	2,578 (85.4%)	<0.001
Respiratory	2,871 (32.9%)	998 (33.1%)	0.89
Short-term mortality			
28-Day mortality	3,888 (44.6%)	958 (31.8%)	<0.001
90-Day mortality	5,335 (61.2%)	1,413 (46.8%)	<0.001

Statistical comparisons were made using the chi-squared test. The threshold for statistical significance was alpha = 5%.

inflammatory properties of statins may play a key role in the observed decrease in ACLF mortality with statin exposure. ACLF is characterised by a severe, systemic inflammatory response, and this hyperinflammatory reaction leads to organ failure and resulting mortality. Therefore, a reduced inflammatory response in patients with statin use may decrease the odds of ACLF related short-term mortality. This potential causal relationship is supported by the reduced degree of leucocytosis in statin-exposed patients in our exploratory analysis, which was observed in both patients with and without infection.

One other plausible mechanism may be in the role of statin therapy in decreasing portal hypertension, likely a result of the antifibrotic and vasoactive properties of statins. Given that statins have been shown to reduce portal hypertension, statin therapy in patients with cirrhosis may decrease the likelihood of portal hypertension-related acute decompensation events leading to ACLF including ascites, hepatic encephalopathy, and some forms of gastrointestinal bleeding, which was observed in the present study. In reducing the likelihood and/or severity of these intrahepatic acute decompensation events, statin therapy may lead to reduced ACLF-related mortality. This hypothesis is consistent with our exploratory analysis demonstrating that the potential benefit of statin exposure is more pronounced in patients with previously compensated cirrhosis. Although speculative, many patients with established decompensated cirrhosis may have degrees of portal hypertension that cannot be adequately mitigated by statin exposure to impact ACLF-related mortality. The plausibility of this mechanism is also in line with our previous study demonstrating the protective association between statin exposure and the development of high-grade ACLF, as patients with prior statin exposure exhibited lower rates of acute decompensation attributable to ascites and hepatic encephalopathy.[8] Finally, we note that in the statin-exposed group, infection was a more likely acute decompensation as compared with the statin-unexposed group. One possible explanation for this is that patients on statins were significantly more likely to have diabetes as compared with those not on statins, as diabetes is well known to increase the risk of infection.[28]

Table 3. Logistic regression models for 28- and 90-day mortality in patients with high-grade acute-on-chronic liver failure by statin exposure.

	28-Day mortality		90-Day mortality	
Variables	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Statin exposure	0.82 (0.73–0.93)	0.001	0.76 (0.68–0.86)	<0.001
Age	1.03 (1.02–1.04)	<0.001	1.03 (1.03–1.04)	<0.001
BMI	0.99 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001
Smoking status		<0.001		0.002
Never smoker	Reference		Reference	
Former smoker	1.05 (0.94–1.16)		1.04 (0.93–1.16)	
Current smoker	1.27 (1.14–1.41)		1.20 (1.08–1.34)	
Aetiology of liver disease		0.001		<0.001
HCV	Reference		Reference	
HBV	1.04 (0.64–1.70)		1.01 (0.61–1.66)	
Alcohol	0.76 (0.66–0.88)		0.65 (0.56–0.76)	
HCV + alcohol	0.91 (0.78–1.07)		0.75 (0.64–0.88)	
NAFLD	0.81 (0.67–0.97)		0.76 (0.63–0.91)	
Other	0.75 (0.53–1.06)		0.69 (0.48–0.97)	
Coronary artery disease	0.83 (0.75–0.92)	0.001	0.83 (0.75–0.92)	0.001
Diabetes mellitus	0.79 (0.72–0.87)	<0.001	0.77 (0.70–0.85)	<0.001
Decompensated cirrhosis	1.19 (1.08–1.31)	0.001	1.41 (1.28–1.55)	<0.001
MELD-Na at admission	1.06 (1.05–1.06)	<0.001	1.05 (1.04–1.05)	<0.001
Serum albumin at admission	0.51 (0.48–0.55)	<0.001	0.50 (0.47–0.54)	<0.001

Wald tests were performed to assess statistical significance of individual covariates. The threshold for statistical significance was alpha = 5%. MELD-Na, model for end-stage liver disease-sodium; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

Table 4. Logistic regression models for 28- and 90-day mortality in patients with high-grade acute-on-chronic liver failure by statin dose exposure.

	28-Day mortality		90-Day mortality	
Variables	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Statin dose (mg)		0.01		<0.001
0	Reference		Reference	
10–40	0.82 (0.71–0.95)		0.81 (0.70–0.93)	
80	0.78 (0.64–0.95)		0.72 (0.60–0.87)	
160	0.88 (0.72–1.07)		0.73 (0.60–0.87)	
Age	1.03 (1.03–1.04)	<0.001	1.03 (1.03–1.04)	<0.001
BMI	0.99 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001
Smoking status		<0.001		0.002
Never smoker	Reference		Reference	
Former smoker	1.04 (0.94–1.16)		1.04 (0.93–1.16)	
Current smoker	1.27 (1.14–1.41)		1.20 (1.08–1.34)	
Aetiology of liver disease		0.001		<0.001
HCV	Reference		Reference	
HBV	1.04 (0.64–1.70)		1.02 (0.62–1.67)	
Alcohol	0.76 (0.66–0.89)		0.65 (0.56–0.76)	
HCV + alcohol	0.91 (0.78–.07)		0.75 (0.64–0.88)	
NAFLD	0.81 (0.67–0.97)		0.76 (0.64–0.91)	
Other	0.75 (0.53–1.06)		0.69 (0.48–0.97)	
Coronary artery disease	0.83 (0.75–0.92)	0.001	0.84 (0.75–0.93)	0.001
Diabetes mellitus	0.79 (0.72–0.87)	<0.001	0.77 (0.70–0.85)	<0.001
Decompensated cirrhosis	1.19 (1.09–1.31)	<0.001	1.41 (1.28–1.54)	<0.001
MELD-Na at admission	1.06 (1.05–1.06)	<0.001	1.05 (1.04–1.05)	<0.001
Serum albumin at admission	0.51 (0.48–0.55)	<0.001	0.50 (0.47–0.54)	<0.001

Wald tests were performed to assess statistical significance of individual covariates. The threshold for statistical significance was alpha = 5%. MELD-Na, model for end-stage liver disease-sodium; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

Finally, our study demonstrated important differences in types of in ACLF between statin-exposed and statin-unexposed groups. We found that statin-exposed patients were much less likely to have classically liver-intrinsic OFs (liver OF, brain OF) and more likely to have kidney OF or circulatory OF, which are more often related to extrahepatic factors. A similar trend was observed in our prior study on statin exposure and development of high-grade ACLF.[8] The beneficial effects of statins on hepatic function and portal hypertension are a plausible explanation of these different organ failure phenotypes, as patients may be relatively more protected against development of liver-intrinsic OFs. Additionally, higher susceptibility to circulatory and kidney OFs in the statin-exposed group may in part be explained by a greater burden of metabolic and cardiovascular disease.

Given the morbidity and mortality associated with ACLF, there is a need for potential therapeutic options that prevent the development of and/or reduce the severity of ACLF events. This study provides additional evidence in support of the potential salutary effects of statins on ACLF. Although concerns regarding hepatoxicity related to statin use have limited their broader prescription in many patients with cirrhosis, it is important to highlight that significant hepatotoxicity is extremely rare, on the order of 2 per 1,000,000 patient-yr.[5,29] Still, the relative safety of statin initiation in patients with more advanced liver disease

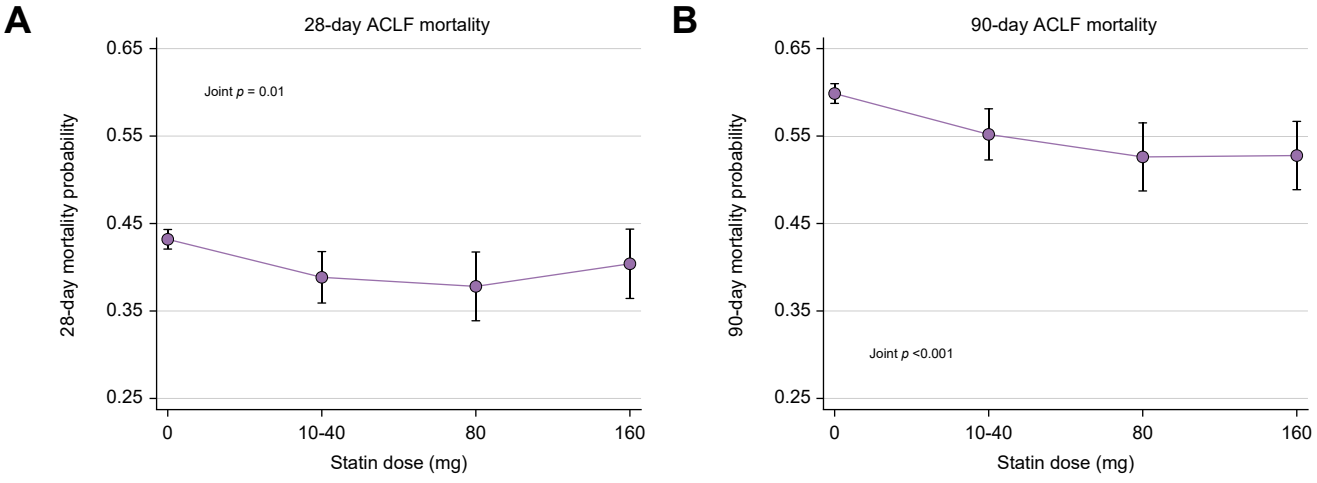

Fig. 1. Association between statin dose and ACLF-related mortality at 28 days and 90 days. (A) Relationship between statin dose and 28-day mortality in adjusted logistic regression model; statistically significant at the 5% level per a joint Wald test (p = 0.01). (B) Relationship between statin dose and 90-day mortality in adjusted logistic regression model; statistically significant at the 5% level per a joint Wald test (p <0.001).

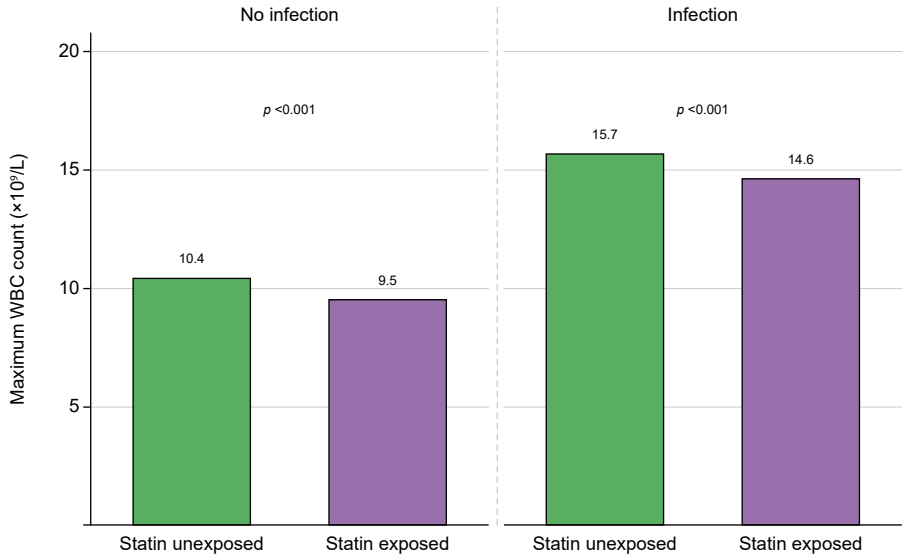

Fig. 2. Maximum white blood cell (WBC) count in statin-exposed and unexposed patients, stratified by infection status. Difference in maximum white blood cell count in statin-exposed *vs.* statin-unexposed patients, separately for patients with and without infection. Both comparisons were statistically significant at the 5% level using Wilcoxon rank-sum testing (p <0.001).

remains unclear. In the LIVERHOPE-SAFETY randomised controlled trial, an increased rate of adverse events including rhabdomyolysis was observed in patients with decompensated cirrhosis who received simvastatin 40 mg *vs.* simvastatin 20 mg.[30] Ultimately, more prospective data are needed to evaluate the safety and efficacy of statin therapy in decompensated cirrhosis including assessments of different classes and doses.

There are several important limitations to note in this study. First, given the nature of a large retrospective study, misclassification of exposures and outcomes is possible. To minimise potential misclassification, we utilised validated algorithms to classify variables wherever possible. However, it is important to acknowledge that there are some inherent limitations in classifying EASL ACLF OFs, including brain failure (active medications plus administrative codes were used as a proxy for high-grade hepatic encephalopathy) and respiratory failure (lack of detailed oxygenation data). Second, this study may be limited in terms of external validity given that this VHA cohort is largely male and with high burdens of comorbid diseases. Third, there is possible selection bias given that patients who previously did not tolerate statins would not have potential for statin exposure in this cohort. This is relevant given the aforementioned data suggesting an increased risk of rhabdomyolysis in patients with decompensated cirrhosis exposed to higher-dose statins, and thus the results of this study should be interpreted only for patients with cirrhosis who have previously demonstrated tolerance for statins. Fourth, our study explored the impact of statins on ACLF utilising EASL–CLIF criteria to define ACLF events. Although EASL–CLIF criteria

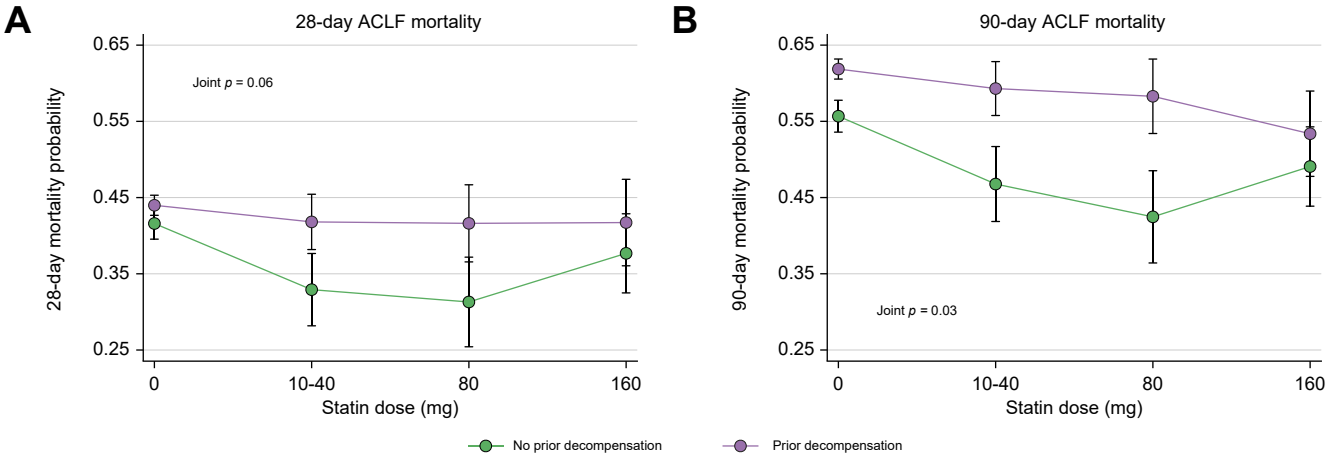

Fig. 3. Changing association between statin dose and acute-on-chronic liver failure (ACLF)-related mortality by cirrhosis decompensation status at 28 days and 90 days. (A) Testing of an interaction between statin dose and decompensation status on 28-day mortality in adjusted logistic regression model; not statistically significant at the 5% level per a joint Wald test (p = 0.06). (B) Testing of an interaction between statin dose and decompensation status on 90-day mortality in adjusted logistic regression model; statistically significant at the 5% level per a joint Wald test (p = 0.03).

for ACLF capture aetiologies of liver disease better represented in this North American cohort, the observed associations may not apply to ACLF adjudicated by other definitions or in cohorts with vastly different epidemiology, such as with predominantly HBV-related cirrhosis. Finally, despite efforts to control for relevant confounding variables in this study, including through a comprehensive IPTW analysis, there is potential for residual confounding. Importantly, the directionality and dose–response of observed effects was generally consistent in all final models. Regardless, it is critical that future prospective studies evaluate and confirm our study findings.

In conclusion, statin exposure was associated with decreased 28-day and 90-day mortality in patients with cirrhosis hospitalised with high-grade ACLF. Moreover, statins were shown to have a dose-dependent association in reducing short-term mortality. Prospective studies are needed to elucidate the potential causal relationship between statins and ACLF-related mortality as well as the safety of this class of medication for patients at various stages of cirrhosis. Future research should also be aimed towards guiding clinical decision-making regarding statin use in patients with decompensated cirrhosis and ACLF.

Abbreviations

ACLF, acute on chronic liver failure; AD, acute decompensation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; CPT, Current Procedural Terminology; CTP, Child-Turcotte-Pugh; EASL–CLIF, European Association for the Study of the Liver–Chronic Liver Failure; ICD, International Classification of Diseases; INR, international normalised ratio; IPTW, inverse probability treatment weighting; LOWESS, locally weighted scatterplot smoothing; MELD-Na, model for end-stage liver disease-sodium; NAFLD, non-alcoholic fatty liver disease; OF, organ failure; OR, odds ratio; PS, propensity score; SMD, standardised mean differences; VHA, Veterans Health Administration; VOCAL, Veterans Outcomes and Costs Associated with Liver Disease; WBC, white blood cell.

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Conflicts of interest

The authors have no additional disclosures or conflicts as relevant to this manuscript.

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

Authors' contributions

Intellectual genesis: NM, SC. Data management: NM, DEK. Formal data analysis: NM, SC. Data visualisation: NM, SC. Manuscript drafting: NM, SC. Critical review of manuscript: NM, SC, TT, DEK.

Data availability statement

The data used in this study were obtained with permission from the United States Veterans Health Administration and are not publicly available.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100740.

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Author names in bold designate shared co-first authorship.

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