



Statin Exposure is Associated with Reduced Development of Acute-on-chronic Liver Failure in a Veterans Affairs Cohort

STUDY SUMMARY

This was a retrospective study that evaluated the association between the risk of developing acute on chronic liver failure (ACLF) in patients with cirrhosis and exposure to statins. The data were collected from the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) cohort.¹ The study included 84,963 patients with cirrhosis. Patients with Fibrosis-4 score² (FIB-4) < 1.45, less than six months of follow-up and less than two outpatient visits in the index year were excluded. Among these patients, 26.9% patients were on statins at baseline. The study estimated the association between time-updated statin exposure and the first occurrence of high-grade ACLF (grade 2 or 3). ACLF was diagnosed and graded using the European Association for the Study of the Liver Chronic Liver Failure (EASL-CLIF) criteria.³ A total of 10.1% (n = 8558) patients were hospitalized with ACLF over a median follow-up period of 51.6 months. Patients with statin exposure had a 38% reduced risk of developing ACLF compared to patients who did not receive statins. There was a significant reduction in the hazard of development of ACLF with time-updated statin use (hazard ratio [HR] 0.62, p < 0.001). The risk of developing ACLF progressively decreased with higher doses of statins (<20 mg vs. >20 mg of simvastatin equivalent doses of statins). Also, the risk of high-grade ACLF became lower with increasing duration of statin exposure and every additional five months of statin exposure was associated with a 9% lower risk of developing high-grade ACLF. Among patients with statin exposure, the most common organ failure was renal failure, and there was a significantly lower incidence of acute decompensation in the form of ascites and encephalopathy in the statin-exposed group. Among patients who developed ACLF, both 28- and 90-day mortality was lower in the statin-exposed group.

DISCUSSION

While statins have been widely prescribed for their cardiovascular benefits, there have been concerns about the safety of statins in liver disease due to concerns of hepatotoxicity, which accounts for the under-prescription of statins in pa-

tients with liver disease. However, while statin use may be associated with elevations in transaminases, these are usually not clinically significant, and significant hepatotoxicity is uncommon.^{4,5} Studies have shown that up to 2% of patients on statins develop a mild-to-moderate elevation in transaminases, though there is no significant liver injury.^{6,7} Even in decompensated liver disease, no significant liver injury has been found with statin use.⁸ There is enough epidemiological and clinical evidence against the misconception that statins are harmful in liver disease.

On the contrary, there has been growing evidence of the role of statins in reducing liver-related adverse outcomes. The potential mechanisms of hepatoprotective effects of statins include an increase in hepatic endothelial nitric oxide synthase and inhibition of hepatic stellate cell activation and cytokine production, which result in decreased hepatic fibrogenesis and reduced portal pressure.^{9,10} Besides, statins induce apoptosis and inhibit angiogenesis and reduce the risk of hepatocellular carcinoma.^{11,12}

A meta-analysis by Kamal et al.¹³ in 2017 showed that the use of statins was associated with reduced fibrosis progression, decompensation, and mortality. However, nine of the ten included studies were observational, and the overall evidence was weak. A multi-center study of the effects of simvastatin on hepatic decompensation and death in subjects presenting with high-risk compensated cirrhosis is currently ongoing.¹⁴

ACLF accounts for 30% of cirrhotic admissions and is associated with high mortality.³ Therapy to reduce the risk of ACLF would improve survival in decompensated liver disease. The current study demonstrates a strong association between statins and reduction in risk of developing high-grade ACLF in patients with cirrhosis, an association which intensified with prolonged statin exposure. There was also a lower incidence of liver failure, encephalopathy, and ascites in the cohort of patients treated with statins suggesting that patients on statins developing ACLF have a different phenotype potentially mediated by the pleiotropic effects of statins on the liver. The current study also demonstrated lower short-term mortality in patients who received statin, though this needs to be established by further observational studies and randomized controlled trials. Statin exposure could also reduce infection-related mortality in ACLF, a concept previously supported by the literature.¹⁵ The higher incidence of kidney and circulatory organ failure in statin-treated patients in the current study may be due to a higher prevalence of underlying of metabolic disease which may have been the

Abbreviations: ACLF: acute on chronic liver failure; ESBL: extended-spectrum beta-lactamase; MDROs: multidrug resistance organisms; VRE: vancomycin-resistant enterococci

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indication for statins. In the current study, the EASL-CLIF definition of ACLF was used. However, if the current observations would apply to other definitions of ACLF is unclear and needs to be studied further.

The current study has the strength of a large cohort but has the inherent weakness of the retrospective design. While statins show promise against the progression of liver disease, more prospective studies are needed to substantiate and establish their role in cirrhosis. Moreover, many questions remain to be answered regarding the choice of statin to be preferred and optimal dosing in patients with decompensated liver disease.

CONFLICTS OF INTEREST

None

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