Statins reduce development of acute-on-chronic liver failure in patients with cirrhosis

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Main Text

Abstract

Acute-on-chronic liver failure can be fatal in patients with cirrhosis, but there are no therapies to prevent this. We summarize the @GIJournal Twitter® discussion held on May 8, 2022, during which we discussed the article by Mahmud et al. titled “Statin exposure is associated with reduced development of acute-on-chronic liver failure in a Veterans Affairs cohort”\(^1\). The session was moderated by Dr. Rohit Mehtani (RM [@RohitMehtaniDM]) and the key findings were critically reviewed by Dr. Nadim Mahmud (NM [@nadimmahmud]) and Dr. Vinay Sundaram (VS [@VinaySundaramMD]).

Introduction

Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome in patients with cirrhosis or chronic liver disease. ACLF is characterized by an acute decompensation event, severe systemic inflammatory response, and one or more organ systems failure (OFs).\(^2\) The outcome of patients that develop ACLF is not good, and more than half die within 90 days.\(^2, 3\) Thus, therapies that prevent or minimize the risk of patients with cirrhosis developing ACLF are urgently needed.

Article Summary

Mahmud et al.\(^1\) retrospectively reviewed patients with cirrhosis within the Veterans Health Administration from 2008 and 2018. The study compared patients not exposed to statins, those that were currently being treated with statins, and patients that were just beginning statin treatment. To determine if the length of statin exposure influenced the development of high-grade ACLF (grade 2 or 3 according to the criteria set forth by the European Association for the Study of the
Liver-Chronic Liver Failure), the authors used inverse probability treatment weighting (IPTW) to simulate a randomized controlled trial and constructed Cox proportional hazards regression models.

Roughly one-quarter of the patients in the study cohort (84,963 patients) were taking statins, and approximately one-tenth of all patients with cirrhosis (8,558 patients) developed high-grade ACLF over a median of 51.6 months (range, 27.5–81.4 months). Analyses associated statin use with a significantly lower probability of ACLF (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.59–0.65; \( p < 0.001 \)), and higher doses progressively reduced the chance of developing ACLF (HR, 0.75 [CI, 0.66–0.86] and 0.61 [0.58–0.64] for <20 mg and >20 mg, respectively; \( p \) values <0.001). Moreover, patients were 9% less likely to develop high-grade ACLF for every additional 5 months that they were treated with statins (HR, 0.91; 95%, CI 0.90–0.92; \( p < 0.001 \)).

This study showed that an additional benefit of statin treatment in patients with chronic liver disease is a reduced probability of developing life-threatening ACLF.

**Discussion**

RM administered a pre-discussion poll on routinely prescribing statins to patients with cirrhosis to decrease portal hypertension, reduce decompensations, and prevent ACLF: most respondents (86.3% [113/131]) chose no, whereas 13.7% (18/131) chose yes.

@SultanMahmoodMD: If anything, statins are stopped as soon as [the patient] is diagnosed with cirrhosis with a concern of “liver damage.”
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@AnandVKulkarni2: For patients with low mean arterial pressure or acute kidney injury and large varices, I start [statin treatment]. It prevents bleeding to some extent, I feel.

RM: Interestingly, this study showed that patients on statins had a higher incidence of renal failure! [This is] possibly related to [the presence of] more atherosclerotic vessels.

@DrArunKValsan: There is enough evidence about the safety of statins. It is logical to use [statins] in patients with other metabolic risk factors that increase the risk of cardiovascular accident/cardiovascular disease/peripheral artery disease. But is there enough data to initiate it to reduce decompensation and for ACLF prevention? I’m unsure today!

@Sanchit30497977: I have my reservations; while I admire and acknowledge the association and plausibility studies for statins in pulmonary hypertension, the randomized studies have shown conflicting evidence, especially with a potent pressure-lowering agent like carvedilol. Statins in decompensated cirrhosis can cause adverse effects; the maximum evidence available is for simvastatin. I guide my clinical decision in ACLD by their cardiometabolic risk factors, not pulmonary hypertension.

RM: Yes. I also feel that currently statins [are] only to be used based on cardiovascular risk factors. More randomized controlled trials are needed!
@drsuniltaneja: I guess statins can be used for nonalcoholic steatohepatitis cirrhosis if the metabolic indication is there. We need more evidence for its use for the reduction of portal hypertension!!

@Montalvan214: [Statins are] usually stopped and [with] comments of “concerns of liver damage.” We probably want them on statins, especially in [patients with] metabolic syndrome-nonalcoholic steatohepatitis.

@AnandVKulkarni2: This article by @jaumebosch9 on statins is a must read.⁴

@Montalvan214: So, can we add statins to daily water intake? [There are] multiple benefits, better assessment tools [are] needed to discontinue them, and [there is a] low threshold to start them.

VS: Ha ha! Not ready yet, but [there is] clear data on safety if otherwise needed.

RM: Q1. The study highlights that patients on statins had a higher incidence of infections as acute precipitant of ACLF. What could be the possible reasons behind this association?

NM: High-grade ACLF was less likely in statin-exposed [patients], but the ACLF phenotypes (in terms of ADs [acute decompensations] and OFs) were different. [It is] speculative, but the reduction in ascites/hepatic encephalopathy ADs may have left infection as the predominant type.
VS: Statins have been shown to reduce portal hypertension

RM: The reduction of ascites/hepatic encephalopathy may have been due to the reduction in portal hypertension due to statins, as @VinaySundaramMD also mentions.

VS: What is also interesting is that the majority of [those that were] statin exposed were NAFLD [nonalcoholic fatty liver disease] patients who have no inherent intrahepatic precipitant. [I'm] wondering if that leads to selection bias leading to this correlation?

VS: …meaning that NAFLD ACLF most likely precipitated from infection and not alcohol use disorder or hepatitis B virus flare. Thus, we are selecting patients who get ACLF from infection.

RM: Yes, quite possible. Most patients with NAFLD would be on statins because of the associated metabolic syndrome. Further randomized trials in other etiologies would make things clear! @nadimmahmud

NM: Very plausible as well; even with advanced inferential methods, [it is] difficult to overcome selection bias and—critically—confounding by indication.

@ChrisAndersonM4: What is the reason to continue statins in the hospital? Do you do it for all patients admitted with liver cirrhosis ACLF or select patients? Do the levels of aspartate transaminase and alanine transaminase make a difference?
VS: I don’t think statins are ready for acute treatment of ACLF. The data are interesting regarding prevention of ACLF and the association with reduced mortality. I would continue [statins] since they are safe but would not start in an inpatient setting.

NM: Agree! Studies are currently ongoing (including from our group) to assess the potential impact of statins on ACLF-related mortality. I do not start statins for ACLF but do not routinely stop [them] if already prescribed for an established indication.

RM: Statins may well be the next nonselective beta-blocker in hepatology!

NM: A limitation of our study if that we were not able to account for concomitant nonselective beta-blocker use. Pharmacoepidemiology studies are very challenging—there are many co-associated variables and complex confounding relationships.

VS: This should be your next study!

NM: Something perhaps tantalizing is under review.

RM: Would you like to continue [statins] even in those ACLF who have liver failure?

VS: In setting of liver failure, I would stop. At this point I don’t think there will be mortality benefit [with statins] and [there is increased] risk of rhabdomyolysis in liver failure
NM: If liver OF would stop for the reasons you mentioned.

@ChrisAndersonM4: What do you think about the argument that the less sick patients probably were already on statins and hence less likely to develop ACLF?

NM: Great question -- Could argue it both ways (eg. Sicker from CV standpoint more likely to be on statin). But methods in this study are designed to account for this as best as possible.

NM: IPTW to balance key covariates at baseline, and adjustment for key time-updated confounders throughout follow-up. No method [is] perfect, however.

RM: Q2. Does addition of statins to beta-blockers lead to additional benefit in preventing decompensation and ACLF, as previously it was shown that simvastatin plus carvedilol does not lead to additional decrease in hepatic venous pressure gradient or prevention of 1st gastrointestinal bleed?[^5]

VS: [There is] no evidence, in my opinion, to support that.

NM: [I] agree with Vinay—insufficient data to support this. However, it would be interesting to see in future studies if there are particular subgroups (liver disease not too advanced) that may benefit.
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**VS:** Exactly! There is no “one size fits all.” Medicine is personalized. ACLF is a highly heterogeneous syndrome, and subgroup analysis is needed.

**RM:** Q3. What could be the reasons behind low incidence of liver and cerebral failure in statin-exposed patients?

**VS:** Interesting questions. For liver failure, I think it’s the precipitant. Yu Shi’s study showed that liver failure is more likely with intrahepatic patients. If patients get an infection (extrahepatic), it leads more likely to extrahepatic OF.

Regarding brain failure, [I] don't have a clear reason.

**NM:** Yes—[I] agree with this 100% as well! Infection-associated ACLF in statin users fits the observed OF profile.

**NM:** Pleiotropic statin effects on liver may reduce the likelihood of OFs that are more “intrinsic to the liver,” including liver OF, brain OF, and coagulation OF. This is precisely what was observed in this study.

**VS:** Interesting idea. We need to consider this versus precipitant.

**RM:** Q4. The IPTW-based propensity score analysis did not include effect of etiology of liver disease on ACLF development. Majority of the patients who were on statins at baseline had
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NAFLD. Could this have any bearing on the finding of differences in the type of organ failure observed?

NM: Perhaps just a point of clarification here—the propensity score used in IPTW did in fact include etiology of liver disease [ref. to figure 2 in Mahmud et al].

I probably just need to work on my figure clarity.

RM: My bad. The Cox regression also included it?

NM: I see the source of confusion! Highlighted variables in the first footnote [ref. to table 3 in Mahmud et al] represent the time-updated covariates adjusted in the Cox model IN ADDITION to applying IPTW.

Apparently, I need to work on my figures and my captions. Noted for next time!

RM: Q5. This study highlights patients on statins less likely to develop ACLF and have reduced mortality once they develop ACLF. Important aspect—should statins be continued once patients develop ACLF considering the risk of hepatotoxicity and rhabdomyolysis in Child-Turcotte-Pugh class C patients?

NM: Great question—in this study, we did not evaluate the association between statin and ACLF-related mortality in great detail (study forthcoming). [It is] not entirely clear how statins should be
managed once ACLF has been diagnosed. For me, it depends on the particulars of phenotype and OFs.

As @VinaySundaramMD pointed out, [I] usually stop [statins] if liver OF is present. More data are needed in this area.

**VS:** Agree here. I would probably stop statins in the setting of liver failure. In the setting of severe ACLF, [I] would not anticipate any beneficial effect.

[@SultanMahmoodMD]: Important clinical question. Also need guidance on dosing. Type of statins? Trigger for stopping?

**VS:** [I] agree, particularly [on] stopping rules. Evidence has focused on proving the safety of statins, but we also need to decide at which point there is no clear benefit and potential for harm.

**NM:** Very important question—I think with advanced liver failure, the dose should be reduced, especially with lipophilic statins such as simvastatin.

For compensated cirrhosis, I generally follow atherosclerotic cardiovascular disease or standard dose guidance based on cardiovascular indications. I'm sure [there are] many others more knowledgeable than me on this!

I try to follow the recommendations of @jaumebosch9.
RM: Q6. *Patients on statins had lower ACLF-related mortality. Was this independent of the severity of ACLF as measured by the Chronic Liver Failure (CLIF) - C ACLF score?*

NM: [It was] not explored in detail in this particular study ([we] only looked at unadjusted analysis); however, we hope our forthcoming data on statins and ACLF-related mortality will be presented in some fashion at AASLD [American Association for the Study of Liver Diseases].

RM: [I’m] looking forward to it!

VS: That will be important. Another interesting thing to look at is whether statin initiation in those recovering from ACLF-1 reduces further ACLF recurrence—particularly in light of your paper showing prior ACLF-1 increases the risk of ACLF-3 in the future.

NM: Not my study—OUR study!?

RM: Key takeaways:

1. Less liver and cerebral failure with statins $\rightarrow$ due to lower portal hypertension?
2. Continue statins after onset of ACLF in patients without liver failure.
3. Avoid starting statins in high-grade ACLF.
4. Dose reduction needed in Child-Turcotte-Pugh class C.
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**VS:** Thanks for the invitation and discussion. It was fun!

**NM:** Thanks for the invitation!

[@GiJournal]: Thanks a lot @VinaySundaramMD, @nadimmahmud, @RohitMehtaniDM, and @Naren_nallapeta.

[@ShimaghavimiMD]: Thank you all. Great session.

**Conclusion**

Mahmud et al.\(^1\) conducted a retrospective study of a large cohort of patients with cirrhosis treated by the Veterans Affairs Administration. They found a significant association between the use of statins (but not non-statin lipid-lowering medications) and reduced development of high-grade ACLF. The probability of developing ACLF was progressively lower with increasing doses and duration of statin therapy. These findings need to be confirmed in prospective studies considering the confounding effect of beta-blockers, and also focus on establishing the safety of statins in patients with decompensated cirrhosis and ACLF. Nevertheless, the current limited evidence suggests that statins mitigate high-mortality ACLF events over time.
REFERENCES


