The Effect of Statin Therapy on Mortality in Adult Patients with Liver Cirrhosis: An Evidence-Based Case Report

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ABSTRACT

***Background*:** *Liver cirrhosis causes over one million deaths annually worldwide, but its prognosis varies depending on the presence of complications and decompensating events. Reduction of portal pressure is associated with a reduced risk of mortality in cirrhotic patients. Statin therapy has successfully reduced portal pressure in previous studies, but its effects on overall mortality are unclear. This report aims to determine whether statin therapy significantly affects mortality in patients with liver cirrhosis.* ***Methods*:** *A comprehensive literature search was conducted using five electronic databases: PubMed, Scopus, Embase, Ovid MEDLINE, and Web of Science. Meta-analyses, randomized controlled trials (RCTs), and cohort studies were selected based on pre-set inclusion and exclusion criteria. The quality of selected studies was evaluated using critical appraisal tools developed by the Center for Evidence-Based Medicine.* ***Results*:** *One meta-analysis, one RCT, and one retrospective cohort study were included in this report. The meta-analysis and cohort study were of good quality and reported significantly reduced mortality with statin therapy in cirrhosis patients. However, the RCT had poor validity and did not report a statistically significant difference in mortality between the intervention and control groups. The survival benefits of statins may be limited to Child–Pugh A and B patients only, but this requires confirmation in a larger population of Child–Pugh C patients.* ***Conclusion*:** *Statins potentially reduce mortality in patients with liver cirrhosis, but more evidence is required before they can be widely recommended in clinical practice for this indication.*

Keywords*: Liver cirrhosis, fibrosis, evidence-based medicine, portal pressure, statins.*

INTRODUCTION

Liver cirrhosis is advanced stage liver disease resulting from chronic damage and necroinflammation of hepatic tissue due to several etiologies, such as viral hepatitis and alcohol-induced toxicity. It is characterized by the presence of regenerative nodules surrounded by networks of thick fibrotic septae, eventually leading to intrahepatic vascular disturbances and loss of hepatocellular function.[1] Liver cirrhosis is the 12th most common cause of death worldwide, claiming more than one million lives annually.[2] Despite this large disease burden, the prognosis of cirrhosis is highly variable; its one-year mortality ranges from 1– 57% depending on the presence of complications and decompensating events.[3]

Portal hypertension is commonly found in cirrhotic patients and is responsible for many complications of cirrhosis.[1] It drives the formation of gastroesophageal varices, and variceal bleeding is associated with a

six-week mortality of 10–20%.[4] It is also responsible for portosystemic shunting of blood, which contributes to the development of hepatic encephalopathy.[5,6] The hyperdynamic circulation in cirrhosis is associated with the development of hepatorenal syndrome and ascites.[1] Decompensation of cirrhosis is defined by the presence of severe complications, including gastrointestinal bleeding, ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy, and is associated with a poor prognosis.[7]

The progression of cirrhosis can be slowed by lifestyle modifications and pharmacological intervention.[1] An important pharmacotherapeutic target in liver cirrhosis is reduction of portal hypertension. A previous meta-analysis reported that a reduction in the portal pressure by ≥ 20% significantly reduces mortality in cirrhotic patients (pooled odds ratio (OR): 0.39, P = 0.012).[8] Current guidelines support the use of non-selective beta blockers (NSBBs) to reduce portal hypertension.[4] However, NSBBs are associated with low hemodynamic response rates and systemic adverse effects.[9-11] Hence, there is a need for other pharmacological agents that can reduce portal pressure. Studies have demonstrated that statins (HMG-CoA reductase inhibitors) can increase intrahepatic nitric oxide (NO) production through upregulation of the transcription factor Krüppel-like factor 2 (KLF-2).[12–14] Reduced intrahepatic NO production by the sinusoidal endothelium contributes to portal hypertension in cirrhosis.[12] Abraldes et al demonstrated that simvastatin increased endothelial nitric oxide synthase (eNOS) expression and activation in cirrhotic rats.[12] Zafra et al reported increased post-prandial hepatic NO products in simvastatin-treated cirrhotic patients.[13] Previous randomized controlled trials (RCTs) on cirrhotic patients report a greater reduction in the hepatic venous pressure gradient (HVPG) with simvastatin administration compared to placebo.[15,16] Aside from reducing portal hypertension, statins are potentially beneficial in cirrhosis by reducing hepatic stellate cell activity and through their immunomodulatory and anti-neoplastic properties. These protective mechanisms are summarized in **Figure 1**.[17,18]

Although statin therapy can reduce portal pressure and exert other potential benefits in liver cirrhosis, it is unclear whether it can improve overall survival in this patient group. Current guidelines do not recommend statin therapy for patients with liver cirrhosis.[4] The aim of this report was to evaluate whether statin therapy can reduce mortality and improve overall survival in adult patients with confirmed liver cirrhosis.

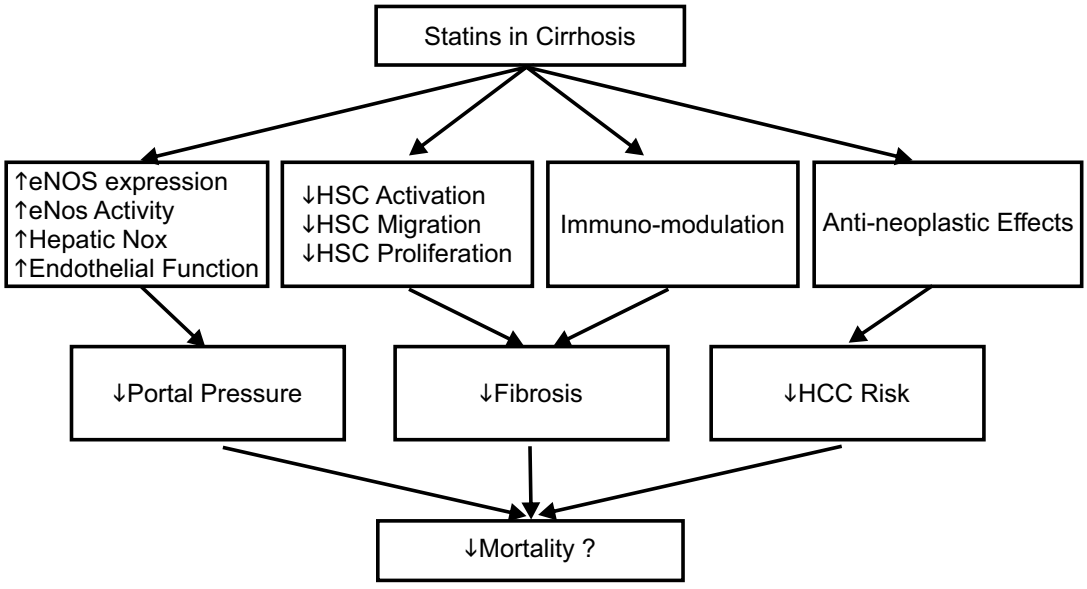

Figure 1. Biological mechanisms of the benefits of statin therapy in cirrhosis[17,18]

CASE ILLUSTRATION

A 39-year-old male patient was admitted with a one week history of massive ascites prior to admission. The patient first experienced ascites two months before admission. At this time, he was diagnosed with hepatitis C with a viral load of three million copies and liver cirrhosis based on abdominal ultrasonography (USG). Since then, the patient was on direct-acting antiviral therapy (sofosbuvir + daclatasvir). One month before admission, esophagogastroduodenoscopy showed esophageal varices (grade 2), large gastric fundal varices, and portal hypertensive gastropathy. At that time, the patient underwent therapeutic paracentesis, but the ascites returned after approximately one week. Since then, the patient experienced refractory ascites and underwent therapeutic paracentesis a total of three additional times with the ascites recurring shortly after each session.

On physical examination, the patient was found to have icteric skin and sclera. The conjunctiva and oral mucosa were pale. The abdomen appeared distended, with distension of the abdominal wall veins. Shifting dullness and fluid wave tests were positive. Bilateral pitting edema was found on the lower extremities. Laboratory examinations showed hyperbilirubinemia (4.41 mg/dL), hypoalbuminemia (2.07 g/dL), hyponatremia (126.0 mEq/L), hyperkalemia (7.0 mEq/L), and reduced kidney function (eGFR: 57.0 mL/min/1.73m^3). Abdominal USG suggested hepatic cirrhosis, splenomegaly, and ascites. The patient underwent therapeutic paracentesis twice during his hospital stay, with persistent massive ascites post-paracentesis.

The patient denied any history of hematemesis, melena, loss of consciousness, or alteration in his behavior or mental state. Based on the available data, the patient's liver cirrhosis was classified as Child-Pugh class C, indicating a poor prognosis and a higher risk of mortality. Currently, pharmacological options that can reduce the risk of mortality in adults with liver cirrhosis are limited. Studies suggest that statins can improve portal hypertension in this population, but their effects on mortality are not well understood.

CLINICAL QUESTION

It is unclear whether statin therapy can reduce mortality in adults with liver cirrhosis, such as in the patient described above. Thus, the following clinical question arose: What is the effect of statin therapy on mortality in adult patients with liver cirrhosis? The patients, intervention, comparison, and outcome (PICO) format for this question was as follows:

- Patients (P): Adults with Liver Cirrhosis
- Intervention (I): Statin Therapy
- Comparison (C): No Statin Therapy
- Outcome (O): Mortality/Survival

METHODS

Search Strategy

To answer the clinical question, a comprehensive literature search was conducted in July 2019 using the following databases: PubMed, Scopus, Embase, Ovid MEDLINE, and Web of Science. The keywords used for the search are presented in **Table 1**.

Eligibility Criteria and Article Selection

The following inclusion criteria were applied in this study: 1) clinical studies on adult patients with confirmed liver cirrhosis; 2) comparison between patients with and without statin therapy; and 3) mortality or survival as an outcome measure. Studies without a specific analysis for baseline cirrhotic patients or studies including only hepatocellular carcinoma (HCC) patients were excluded. The types of studies included were meta-analyses, systematic reviews, RCTs, and cohort studies. Inclusion was not restricted by year of publication, sample size, or language.

Critical Appraisal

The quality of selected studies was evaluated using critical appraisal tools available from www.cebm.net developed by the Center for Evidence-Based Medicine (CEBM) at the University of Oxford.[19] Critical appraisal was conducted by both authors independently. Any differences in judgement were discussed among both authors before the final decision was made.

Data Extraction

The data extracted from each study included the study population, details of statin therapy, and

Table 1. Electronic databases and keywords used in the search.

Database Used	Search Strategy and Keywords Used
PubMed	(((cirrhosis[Title/Abstract] OR cirrhotic[Title/Abstract])) AND (mortality[Title/Abstract] OR survival[Title/Abstract] OR prognosis[Title/Abstract] OR death[Title/Abstract])) AND (statin[Title/Abstract] OR atorvastatin[Title/Abstract] OR fluvastatin[Title/Abstract] OR simvastatin[Title/Abstract] OR lovastatin[Title/Abstract] OR pitavastatin[Title/Abstract] OR pravastatin[Title/Abstract] OR rosuvastatin[Title/Abstract])
Scopus	TITLE-ABS-KEY (cirrhosis OR cirrhotic) AND TITLE-ABS-KEY (mortality OR survival OR prognosis OR death) AND TITLE-ABS-KEY (statin OR atorvastatin OR fluvastatin OR simvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin)
Embase	1. (cirrhosis or cirrhotic).ab,kw,ti. 2. (mortality or survival or prognosis or death).ab,kw,ti. 3. (statin or atorvastatin or fluvastatin or simvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin).ab,kw,ti. 4. 1 and 2 and 3
Ovid MEDLINE	1. (cirrhosis or cirrhotic).ab,kw,ti. 2. (mortality or survival or prognosis or death).ab,kw,ti. 3. (statin or atorvastatin or fluvastatin or simvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin).ab,kw,ti. 4. 1 and 2 and 3
Web of Science	#1: ALL=(cirrhosis OR cirrhotic) #2: ALL=(mortality OR survival OR prognosis OR death) #3: ALL=(statin OR atorvastatin OR fluvastatin OR simvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin) #4: #1 AND #2 AND #3

survival outcomes. Both authors conducted data extraction independently. Any disagreements were discussed among both authors before the final decision was made.

RESULTS

Search Results

Figure 2 shows a Preferred Reporting Items for a Systematic Review and Meta-Analysis style flowchart outlining the sequential steps applied in the selection of studies. A total of eight articles were considered relevant based on the selection criteria. Of these, the meta-analysis by Kim et al included five of the other relevant articles identified.[20] Hence, this meta-analysis, along with an RCT by Bishnu et al[21] and a retrospective cohort study by Kaplan et al[22] were selected for further analysis.

Kim et al conducted a meta-analysis of one RCT and four retrospective cohort studies.[20] Bishnu et al randomized 30 consecutive patients with confirmed liver cirrhosis to receive either NSBBs with atorvastatin or NSBBs alone.[21] The retrospective cohort study by Kaplan et al evaluated the effect of statin therapy on mortality in patients with confirmed liver cirrhosis. Their cohort consisted of 21,921 patients receiving statin therapy at baseline and 53,063 patients without baseline statin therapy (i.e., a statin naïve group). Within the statin naïve group, the authors conducted a subgroup analysis where each statin initiator (i.e., each patient who started statin therapy during follow-up) was matched and compared to two statin non-initiators (i.e., patients never treated with statins throughout follow-up). From this subgroup analysis, information about the effect of cumulative statin therapy was extracted. Comparisons in mortality between statin non-initiators and statin initiators at baseline were also extracted.[22]

Critical Appraisal

All three selected articles were critically appraised for validity, importance, and applicability using tools developed by the CEBM.[19] Since there were different types of studies, appropriate tools were selected for each study. The validity of selected studies is presented in **Table 2**.

The studies conducted by Kim et al and Kaplan et al were well designed and sufficiently valid.[20,22] However, the RCT by Bishnu et al had reduced validity and was prone to significant bias.

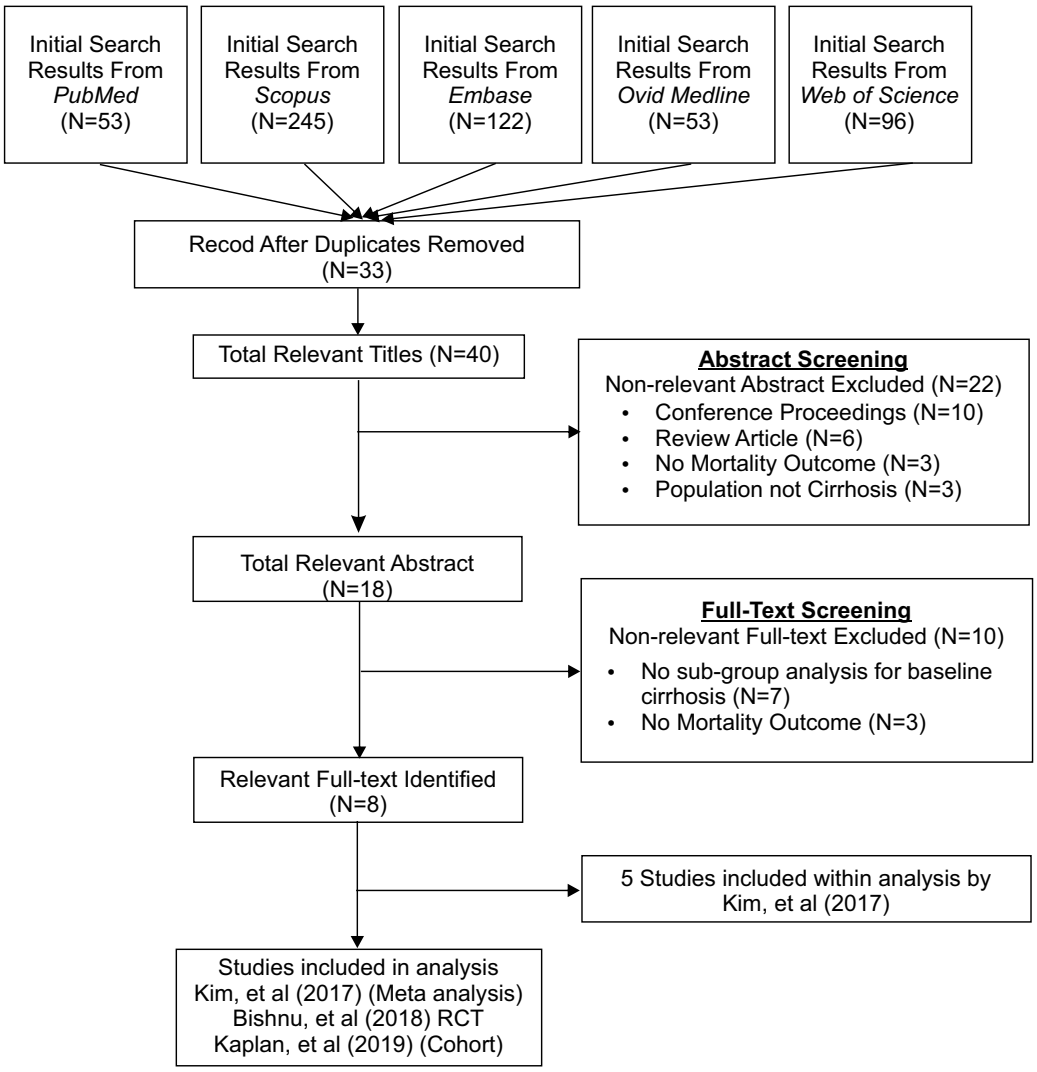

Figure 2. The results of electronic database searches and study selection.

Table 2. Validity of selected studies.

Kim et al (Meta-Analysis)		Bishnu et al (RCT)		Kaplan et al (Retrospective Cohort)	
Was the main question being addressed clearly stated?	Yes	Was the assignment of patients to treatments randomized?	Yes	Was the defined representative sample of patients assembled at a common point in the course of their disease?	Yes
Is it unlikely that important, relevant studies were missed?	Yes	Were the groups similar at the start of the trial?	Yes	Was patient follow-up sufficiently long and complete?	Yes
Were the criteria used to select articles appropriate?	Yes	Aside from the allocated treatment, were groups treated equally?	Yes	Were outcome criteria either objective or applied in a 'blind' fashion?	Yes
Were the included studies sufficiently valid for the type of question asked?	Yes	Were all patients who entered the trial accounted for? And were they analyzed in the groups to which they were randomized?	No	If subgroups with different prognoses were identified, did adjustment for important prognostic factors take place?	Yes
Were the results similar from study to study?	Yes	Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	No		

In this open-label trial, neither the investigators nor the participants were blinded to group allocation. In addition, 23.3% of this study's population was lost to follow-up (3/15 in the control group and 4/15 in the treatment group) without an intention-to-treat analysis.

According to the CEBM critical appraisal tools, the importance of each study refers to the size and precision of treatment effects, which is denoted by a relative risk (RR) or hazard ratio (HR) and confidence intervals (CIs). This information is presented in the Data Extraction section. All three studies are applicable to the patient described in this case report, as they only included patients with confirmed liver cirrhosis. Treatment with statins is feasible in clinical practice, as these drugs are widely available at a relatively low cost.

Data Extraction

From each study, data about the study design and population, statin therapy, and mortality outcomes were extracted. These data are presented in **Table 3**.

DISCUSSION

A total of three studies answering the clinical question were identified. The meta-analysis by Kim et al[20] represents the highest level of evidence and was sufficiently valid (**Table 2**).[20] Although RCTs represent a high level of evidence, the trial by Bishnu et al had poor validity due to its open-label design and high drop-out rates (**Table 2**).[21] The retrospective cohort study by Kaplan et al represents a lower level of evidence than the other studies but is valuable because of its large sample size and good internal validity (**Tables 2 and 3**).[22]

Table 3 shows generally favorable mortality outcomes with statin therapy in liver cirrhosis patients. The meta-analysis by Kim et al reported a 46% reduction in mortality with statin therapy based on a pooled analysis from one RCT and four retrospective cohort studies (pooled RR: 0.54, P<0.05).[20] This finding was supported by Kaplan et al, who reported significantly reduced mortality with a cumulative annual statin therapy (HR: 0.913, P<0.0001). They also reported that patients using statins at baseline had reduced mortality compared to patients who were never treated with statins (HR: 0.943, p<0.05).[22] In contrast, Bishnu et al reported no statistical difference in mortality between the intervention and control groups.[21] However, this study was an open-label proof-of-concept RCT with a primary

Table 3. Study designs and main findings.

Study	Study Population	Intervention and Control	Mortality Outcomes
Kim et al (Meta-Analysis)	Four retrospective cohort studies and one RCT included. Total number of patients in the mortality analysis: N = 8,017	Statin therapy (intervention) vs no statin therapy (control)	**Pooled relative risk for all-cause mortality**: 0.54 (95% CI: 0.47–0.61) with statin therapy in liver cirrhosis patients
Bishnu et al (RCT)	30 patients with evidence of portal hypertension were analyzed	Patients were randomized to receive 40 mg propanolol + 20 mg atorvastatin daily (intervention) or 40 mg propanolol only (control) for 30 days.	At a one-year follow-up, 1/12 patients died in the control group (8.33%) and 0/11 patients died in the intervention group. **(chi-square p=1.000)**
Kaplan et al (Retrospective Cohort Study)	A total of 74,984 patients were analyzed. There were 21,921 baseline statin users and 53,063 baseline statin naïve patients. Of the patients in the baseline statin naïve group, 8,794 patients received statin therapy during follow-up (statin initiators) and 44,269 never received statin therapy during follow-up (statin non-initiators).	Baseline statin users were compared with statin non-initiators Subgroup analysis: within statin naïve group, 6,481 statin initiators and 12,860 matched statin non-initiators were compared. The effect of cumulative statin therapy per-year on mortality was analyzed.	**Baseline statin users vs statin non-initiators:** HR: 0.943 (95% CI: 0.926–0.971, p<0.05) **Statin initiators vs statin non-initiators:** HR: 0.913 (95% CI: 0.890–0.936, p<0.0001) (with cumulative per-year statin therapy)

RCT, randomized controlled trial; HR, hazard ratio; CI, confidence interval.

outcome measure of HVPG reduction and not mortality. The initial sample size in each group was small (N=15) with a significant overall loss to follow-up (23.3%). No sample size or power calculation was conducted prior to the study. Hence, this RCT has a high risk of bias, and its results must be interpreted with caution.

A retrospective cohort study by Chang et al reported that within the statin group, a cumulative defined daily dose of 28 vs 28–365 vs > 365 had associated HRs of 1 vs 0.61 vs 0.24, respectively (overall P<0.0001).[23] This dose-dependent pattern strengthens the evidence for mortality benefits with statin therapy in liver cirrhosis patients. This study was included in the meta-analysis by Kim et al.[20]

Evidence suggests that the survival benefits of statins may be limited to Child-Pugh class A and B patients only. An RCT by Abraldes et al demonstrated that statin administration significantly reduced mortality in Child-Pugh class A and B patients (P=0.006) but not in Child-Pugh class C patients (P=0.295).[24] Similarly, Kaplan et al found that cumulative statin therapy significantly reduced mortality in Child-Pugh A (P<0.0001) and Child-Pugh B (P=0.0005) patients but not in Child-Pugh C patients (P=0.64).[22] This finding suggests that statins may be more beneficial in patients in early stages of cirrhosis. However, the number of Child-Pugh C patients in both studies was significantly fewer than that of Child-Pugh A and B patients (23 vs 124 in Abraldes et al and 130 vs 20,211 in Kaplan et al). Hence, this observation could be due to the small sample size of Child-Pugh C patients leading to insufficient power to reach statistical significance.

The main proposed mechanism for mortality reduction with statin therapy in liver cirrhosis patients is reduction of portal pressure. Statins achieve this by upregulating KLF-2, increasing expression and activation of eNOS, and increasing intrahepatic NO levels.[12–14,17] Portal hypertension is associated with the development and bleeding of gastroesophageal varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy.[25] Three RCTs have reported significantly reduced portal pressure with statin therapy compared to control groups.[15,16,21] A reduction in portal pressure is associated with a reduced risk of variceal bleeding, re-bleeding, and overall mortality.[8]

Statins could also reduce mortality by preventing serious infections, HCC, and hepatic decompensation.[26] The occurrence of infections in cirrhosis increases the risk of kidney injury, hepatic encephalopathy, and mortality. A large population-based study reported that statins were associated with a reduced incidence of hospital-associated infections (HR: 0.67; 95% CI: 0.47-0.95) through unknown mechanisms.[27] A meta-analysis reported that statins were associated with a reduced risk of progression to HCC in chronic hepatitis C patients (pooled RR: 0.45, P=0.021),[28] which is possibly due to their anti-neoplastic effects.[18] In addition, the meta-analysis by Kim et al demonstrated significantly reduced rates of hepatic decompensation with statin therapy in chronic liver disease and liver cirrhosis patients.[20]

The primary concern with statin administration in patients with liver disease is safety, since statins undergo first pass metabolism and can elevate liver enzymes.[26] However, studies have shown that statins are well-tolerated in patients with chronic liver disease.[29,30] Previous RCTs on patients with compensated liver cirrhosis reported no differences in adverse effects and liver enzyme elevation with or without statin administration.[15,16] Nevertheless, an RCT on decompensated cirrhosis patients reported an increased risk of rhabdomyolysis with simvastatin administration.[24] The National Lipid Association's Safety Task Force concluded that statins are not contraindicated in chronic liver disease or compensated cirrhosis but must be used with caution in decompensated cirrhosis patients.[31]

Statins are widely available at a relatively low cost. Moreover, the benefits of statins are suggested to be additive to NSBBs in cirrhosis.[32] If proven to be effective and safe, the addition of statins could be a feasible and cost-effective solution to decelerate the progression of cirrhosis. Cost-effectiveness is of additional importance in developing economies, such as Indonesia, which is currently in transition toward universal health coverage through its national insurance program,

Jaminan Kesehatan Nasional.

The main limitation of this evidence-based case report is the scarcity of high level evidence. Cohort studies, especially retrospective cohort studies, are prone to bias, and represent a lower level of evidence than RCTs and meta-analyses. Although meta-analyses represent the highest level of evidence, the study by Kim et al consisted of four retrospective cohort studies and one RCT. Hence, most of the current data on statins and mortality in cirrhosis patients comes from retrospective cohort studies, which are inferior to prospective cohort studies and RCTs. More high quality studies are required before statin administration can be widely recommended for cirrhosis patients in daily clinical practice.

CONCLUSION

The current evidence suggests that statin therapy is potentially beneficial in reducing mortality in liver cirrhosis patients. This benefit seems to be limited to Child-Pugh class A and B patients; however, this benefit must be confirmed in a larger cohort of Child-Pugh C patients. High quality prospective cohort studies and RCTs are required to confirm the survival benefits of statin therapy in cirrhosis patients before they can be widely recommended.

Our patient had advanced stage Child-Pugh class C cirrhosis with refractory ascites, which suggests decompensation. The current evidence suggests that the benefit and safety profile of statin therapy for decompensated liver cirrhosis is unfavorable. Hence, statin therapy was not recommended for this patient.

CONFLICTS OF INTEREST

The authors of this study state that they have no conflicts of interest.

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