Dear Editors and Reviewers,

Thank you for taking the time to review our manuscript. We appreciate your insightful comments and are grateful for the opportunity to improve our work. Our point-by-point response is provided below.

**Reviewer 1**

**Reviewer Comment: In this paper, the authors focused on summarizing the pharmacotherapy for the prevention of decompensation in patients with compensated liver cirrhosis, which provided a direction for the further research of pharmacotherapy in these patients.**

Author Response: Thank you for taking the time to review our manuscript. We appreciate your encouraging feedback.

**Reviewer 2**

**Reviewer Comment: It would be necessary for the authors to add information about the doses of the drugs analyzed in this report, at least the doses used in every RCT. So please add the doses of propranolol, nadolol, or carvedilol used on the different RCTs cited in the bibliography. The same is true for statins.**

Author Response: Thank you for raising this point. We agree that it is important to be as specific as possible. Thus, we have added drug doses in the instances in which they were not previously specified. The following excerpts represent the modified versions:

“The landmark trial demonstrating the utility of NSBBs in preventing decompensation was the Study on Beta-Blockers to Prevent Decompensation of Cirrhosis with Portal Hypertension (PREDESCI). In this multicenter, double-blind, randomized controlled trial (RCT), 201 patients with compensated cirrhosis and clinically-significant portal hypertension (CSPH) without high-risk varices were randomized to receive NSBBs (propranolol up to 160 mg twice daily or carvedilol up to 25 mg daily) or placebo.”

“Pascal et al. found that patients receiving propranolol up to 320 mg daily were less likely to develop bleeding episodes compared to those in the placebo group (74% versus 39%; $P < 0.05$); Ideo et al. also observed significantly lower rates among those receiving nadolol up to 120 mg daily (94.4%) relative to those receiving placebo (70.2%).”

“Notably, however, the Prevention of Esophageal Varices by Beta-Adrenergic Blockers trial observed no differences in the use of timolol up to 80 mg daily versus placebo in the development of varices among patients with compensated cirrhosis.”

“In comparing carvedilol to variceal band ligation, one study found carvedilol 12.5 mg daily to be associated with significantly lower rates of initial variceal hemorrhage (HR 0.41, 95% CI 0.19-0.96; $P = 0.04$) but similar rates of bleeding-related and overall mortality, while another reported comparable rates across all three outcomes with the same dosing.”

“Most notably, in a post-hoc analysis of a RCT comparing rifaximin 550 mg twice daily to placebo, Flamm et al. demonstrated that rifaximin reduces the risk for further hepatic decompensation (HR 0.41, 95% CI 0.25–0.67; $P < 0.001$).”

"In a RCT of patients with advanced cirrhosis randomized to receive enoxaparin 4000 IU/day or no treatment, decompensation was significantly less common among those receiving enoxaparin (11.7% versus 59.4%; P < 0.0001)."

"A prospective trial demonstrated that the addition of spironolactone 100 mg daily to nadolol reduced the risk of a combined endpoint of variceal hemorrhage and ascites (39% vs. 20%; P < 0.04)."

"Although the primary outcome was mortality, secondary analyses demonstrated that weekly 40-gram albumin infusions reduced the risk for refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy in comparison to standard medical therapy alone."

In some cases, we had already specified drug doses as noted in the following example:

"In the United States, the Statins and Cirrhosis: Reducing Events of Decompensation (SACRED) trial is studying simvastatin at a dose of 40 mg daily (ClinicalTrials.gov, NCT03654053). In Denmark, the Statins for Prevention of Disease Progression and Hospitalization in Liver Cirrhosis (STATLiver) trial is studying atorvastatin at doses of 10-20 mg daily (ClinicalTrials.gov, NCT04072601)."

**Reviewer 3**

**Reviewer Comment: The authors wrote in details about portal hypertension and prophylactic beta blockers although these medications have no role to prevent decompensation directly, these should be summarized and written in concise way.**

Author Response: Non-selective beta-blockers do have a direct role in preventing hepatic decompensation based on the findings of the PREDESCI trial, among other

studies. Currently, these drugs are the mainstay for chemoprevention in portal hypertension. We have summarized the relevant data. Here are some notable excerpts:

> "The landmark trial demonstrating the utility of NSBBs in preventing decompensation was the Study on Beta-Blockers to Prevent Decompensation of Cirrhosis with Portal Hypertension (PREDESCI)…Over a median follow-up of 37 months, the risk of hepatic decompensation, including ascites, variceal hemorrhage, or hepatic encephalopathy, was significantly lower among patients receiving NSBBs relative to those receiving placebo (HR 0.51, 95% CI 0.26-0.97; P = 0.041). This difference was driven primarily by a reduction in ascites (HR 0.42, 95% CI 0.19-0.92; P = 0.03), although non-significant trends towards decreased progression to high-risk varices and improved survival were also observed."

> "Furthermore, other RCTs have demonstrated the efficacy of propranolol or nadolol specifically for the prevention of variceal hemorrhage among patients with cirrhosis and large esophageal varies but without prior bleeding episodes. Pascal et al. found that patients receiving propranolol up to 320 mg daily were less likely to develop bleeding episodes compared to those in the placebo group (74% versus 39%; P < 0.05); Ideo et al. also observed significantly lower rates among those receiving nadolol up to 120 mg daily (94.4%) relative to those receiving placebo (70.2%)."

> "The potential benefits of carvedilol beyond those of traditional NSBBs have also been of great interest. Four RCTs have evaluated the impact of carvedilol in preventing decompensation among patients with compensated cirrhosis and CSPH…Additionally, a recent meta-analysis of these four studies observed a significantly improved hazard ratio for decompensation among patients receiving carvedilol compared to control therapy (HR 0.506, 95% CI 0.289-0.887; P = 0.017)."

**Reviewer Comment: The authors neglected drugs like anti-viral drugs that have potent direct and critical role in prevention of decompensation and removal of cirrhotic patients from transplant list based on their efficacy in improving cirrhosis and also corticosteroids and other therapies for autoimmune hepatitis.**

Author Response: In our manuscript, we discuss traditional treatment strategies such as risk factor modification pertaining to the three most common causes of cirrhosis. We specifically discuss the role of direct-acting antiviral agents for chronic hepatitis C virus infections. The excerpt is as follows:

"Among patients with chronic HCV infection and compensated disease, the advent of direct-acting antiviral agents represents a landmark achievement that has been shown to reduce the risk for liver-related complications. Unfortunately, more than 40% of HCV infections are diagnosed after hepatic decompensation has already occurred, at which point antiviral treatment is less effective and associated with a higher risk for adverse events."

However, the primary aim of this review is to discuss emerging therapies aimed at preventing hepatic decompensation regardless of disease etiology. The purpose is not to revisit traditional treatment options for each type of chronic liver disease – such reviews have been done in the past and this would be beyond the scope of our manuscript. Regardless, we have added the following concise statement in an effort to be more complete:

"For patients with less common causes of chronic liver disease, risk factor modification may include therapies such as immunosuppression (autoimmune hepatitis), ursodeoxycholic acid (primary biliary cholangitis), and phlebotomy or chelation (hemochromatosis). Unfortunately, the impact of some of these treatments is generally diminished in the context of cirrhosis."

**Reviewer Comment: The manuscript is in need for major language edition.**

Author Response: Both authors are primary English language speakers. We have thoroughly checked the manuscript for any grammar mistakes.

**Revision reviewer**

**Reviewer Comment: No specific comments.**

Author Response: Thank you for your comments.