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Commentary

Carvedilol and the evolving management of portal hypertension in compensated cirrhosis

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Abstract

Cirrhosis remains a major cause of liver-related mortality worldwide. The transition from compensated to decompensated disease, marked by complications such as ascites, hepatic encephalopathy, or variceal hemorrhage represents a critical shift in prognosis and survival. Clinically significant portal hypertension (CSPH) is the primary driver of this progression, making portal pressure reduction a central therapeutic target.

For decades, non-selective beta-blockers (NSBBs) such as propranolol and nadolol have been used to lower portal pressure by reducing cardiac output and splanchnic blood flow. Carvedilol has recently emerged as a promising alternative because, in addition to β-adrenergic blockade, it also antagonizes α1 receptors, leading to intrahepatic vasodilation and greater reductions in hepatic venous pressure gradient.

This commentary discusses the findings of a recent propensity score matched cohort study by Almasri *et al*., which compared carvedilol and propranolol in patients with compensated cirrhosis using a large real-world U.S. database. The study demonstrated a lower incidence of hepatic decompensation among patients receiving carvedilol and suggested a modest reduction in long-term mortality, although hospitalization rates were higher.

These findings support a growing body of evidence favoring carvedilol as a first-line agent for portal hypertension. While observational data are increasingly compelling, randomized trials powered for clinical outcomes are still needed to definitively establish the optimal beta-blocker strategy in compensated cirrhosis.

Keywords: Cirrhosis, Portal hypertension, Carvedilol, Non-selective Beta-blockers, Hepatic decompensation

Introduction

Cirrhosis is the leading cause of liver related death, with a steady increase in mortality since 2009 [1,2]. Transition from compensated to decompensated cirrhosis marks a dramatic shift in prognosis and leads to a marked reduction in life expectancy [3]. It is estimated that the one-year mortality rate is 5.4% in compensated cirrhosis and 20.2% in decompensated cirrhosis [4]. The cardinal manifestations that define decompensation are ascites, hepatic encephalopathy, and variceal hemorrhage [5].

Portal hypertension, especially clinically significant portal hypertension (CSPH), is the strongest predictor of this progression, and is the most common complication of cirrhosis [6,7]. CSPH is defined as a portal pressure of ≥10 mm Hg – typically measured by the hepatic venous pressure gradient (HVPG) – as both varices and decompensation may occur after reaching this threshold [6,8].

Non-selective beta blockers (NSBBs) have long been the cornerstone of therapy in the management of portal hypertension in cirrhosis [7,9]. They reduce portal venous inflow, which is increased in clinically significant portal hypertension, by decreasing cardiac output through β1-adrenergic blockade, and by inducing splanchnic vasoconstriction through β2 blockade [10–12]. These mechanisms lead to a reduction in portal pressure. Long term therapy with these agents improves decompensation free survival and reduces liver related mortality [12]. This benefit is attributable to their role in decreasing the likelihood of developing ascites – the most common decompensating event [12]. The development of ascites carries an estimated 2-year mortality rate of up to 50% [13].

Traditionally, classical NSBBs (cNSBBs) i.e., propranolol and nadolol, have been used. However, in recent years, carvedilol has increasingly been favored due to its greater portal pressure-lowering effect and emerging evidence suggesting improved clinical outcomes compared with traditional non-selective beta-blockers [10,11,14]. This is partly due to the dual mechanism of action of the drug, being able to block alpha 1 adrenergic receptors along with beta receptors [15], resulting in its greater HVPG reducing effect than propranolol [16,17].

This commentary expands on the findings of a recently published retrospective cohort study by Alamasri *et al.*, which used propensity score matching (PSM) to compare carvedilol and propranolol for the prevention of decompensation in patients with compensated cirrhosis. Previous studies have been limited by small sample sizes, short follow up periods, or single center designs. In contrast, this study provides important clinical insights as it incorporates a diverse multi-institutional US based cohort, providing real world clinical data with long follow up duration [18].

Methods

The authors conducted a retrospective cohort study using the US Collaborative Network within the TriNetX database. The International Classification of Diseases, Tenth Revision (ICD-10), procedure codes, and RxNorm medication codes were used to identify clinical variables. Cohorts consisted of adult patients (aged ≥ 18 years) diagnosed with compensated cirrhosis, prescribed either propranolol or carvedilol, between January 1, 2008, and December 31, 2020. The ICD-10 code K74 which correlated to 'Fibrosis and Cirrhosis of the Liver' was used to define compensated cirrhosis. Patients with any history of a decompensating event, including ascites, variceal bleed, hepatic encephalopathy, jaundice, spontaneous bacterial peritonitis, hepatorenal syndrome, portal vein thrombosis, hepatopulmonary syndrome, hepatocellular carcinoma, and a history of liver transplant before the index event (i.e., NSBB initiation date) were excluded. Two cohorts – one for patients taking carvedilol, and the other propranolol – were created.

One-to-one propensity score matching (PSM) was performed to balance out differences in demographics, co-morbidities, and laboratory values among the two groups. Demographics included age, sex, race, ethnicity, and body mass index. Co-morbids, selected using the Charlson Comorbidity Index (CCI), included hypertension, diabetes mellitus, ischemic heart disease, heart failure, cerebrovascular disease, chronic kidney disease, peripheral vascular disease, dementia, chronic obstructive pulmonary disease, and human immunodeficiency virus infection. To account for liver disease severity, MELD score components (creatinine, bilirubin, INR) and additional laboratory markers (platelet count, albumin, AST, ALT, sodium, hemoglobin) were included in PSM by the authors.

Outcomes included development of ascites, variceal bleeding, hepatic encephalopathy at one and five years from the index event. At the 5-year interval, the authors also included hepatorenal syndrome, spontaneous bacterial peritonitis, 5-year all cause hospitalization and 5-year all-cause mortality as outcomes. Furthermore, five-year outcome analysis on the unmatched cohorts was performed to reduce the potential bias introduced by PSM. Statistical analysis and propensity score matching was conducted using the built-in software within the TriNetX database. Logistic regression analysis was performed to generate odds ratios (OR) with 95% confidence intervals (CIs) for each outcome. P values less than 0.05 were considered statistically significant [18].

Results

The study by Almasri *et al.*, after matching, included 12,890 patients in each group, at the one-year interval, the incidence of hepatic encephalopathy was significantly decreased in the carvedilol cohort. However, there was no significant difference in the incidence of ascites and variceal bleed between the two cohorts [18].

At 5-year interval – both before and after PSM – the analysis revealed a significant reduction in the development of any decompensating event (i.e., ascites, variceal bleed, hepatic encephalopathy, hepatorenal syndrome), and a significantly higher rate of all cause 5-year hospitalization in the carvedilol cohort compared to propranolol. All cause 5-year mortality was significantly higher in the carvedilol group before propensity score matching. However, after matching, a marginal reduction in 5-year mortality was seen. There was no significant difference between the rates of spontaneous bacterial peritonitis both before and after PSM in both groups. **Table 1** outlines the main findings of the study [18].

Shifting paradigm in portal hypertension management

Non-selective beta-blockers have been used for the primary and secondary prophylaxis of variceal hemorrhage since 1981, when Lebrec *et al.* illustrated the efficacy of propranolol in reducing portal pressure [19]. The landmark study by Villanueva *et al.* changed this approach by illustrating that NSBBs could not only prevent variceal bleed but also have a beneficial role in preventing any decompensating event, mainly by reducing portal hypertension in parents with cirrhosis [12]. It is estimated that for every 1 mmHg increase in HVPG above a threshold level of 10 mmHg, an 11% increase in the risk of clinical decompensation could be expected [20]. As mortality in decompensated cirrhosis is significantly higher than in compensated cirrhosis [4], the need to effectively reduce the HVPG, and hence portal pressure, is imperative.

In recent years, several studies have supported the superior efficacy of carvedilol [10–12] due to its ability to significantly decrease the hepatic venous pressure gradient (HVPG) compared to other NSBBs [10]. The latest Baveno VII consensus conference, and the 2023 American Association for the Study of Liver Diseases (AASLD) both suggest carvedilol as the preferred NSBB of choice for managing portal hypertension due to superior tolerance and potential ascites reduction [10,11]. While previous studies demonstrating carvedilol's superiority over other cNSBBs are promising, most rely on clinically impractical surrogate markers such as hepatic venous pressure

Table 1. Results of first decompensation events between carvedilol and propranolol cohort.

Outcomes	Carvedilol n (%)	Propranolol n (%)	Odds Ratio (95% CI)	p
One year outcome analysis after propensity score matching				
Ascites	440 (3.83)	479 (4.18)	0.913 (0.800, 1.042)	0.178
Variceal bleeding	105 (0.83)	98 (0.77)	1.078 (0.818 1.421)	0.594
Hepatic encephalopathy	490 (4.16)	547 (4.96)	0.831 (0.735, 0.940)	0.003
Five-year outcome analysis before propensity score matching				
Ascites	1,980 (7.61)	1,328 (9.96)	0.745 (0.692, 0.801)	<0.001
Variceal bleeding	335 (1.18)	333 (2.26)	0.519 (0.445, 0.605)	<0.001
Hepatic encephalopathy	1,958 (7.35)	1,413 (10.46)	0.679 (0.632, 0.730)	<0.001
Hepatorenal syndrome	219 (0.77)	194 (1.29)	0.588 (0.484, 0.714)	<0.001
Spontaneous bacterial peritonitis	486 (1.71)	259 (1.74)	0.984 (0.845, 1.146)	0.838
All cause 5-year hospitalization	4,620 (26.56)	2,102 (19.91)	1.455 (1.372, 1.542)	<0.001
All cause 5-year mortality	5,524 (19.29)	2,264 (15.10)	1.344 (1.274, 1.418)	<0.001
Five-year outcome analysis after propensity score matching				
Ascites	1,019 (8.87)	1,127 (9.84)	0.893 (0.817, 0.976)	0.012
Variceal bleeding	215 (1.71)	273 (2.16)	0.788 (0.658, 0.944)	0.010
Hepatic encephalopathy	1,036 (8.80)	1,218 (10.53)	0.819 (0.751, 0.894)	<0.001
Hepatorenal syndrome	122 (0.95)	175 (1.36)	0.694 (0.550, 0.876)	0.002
Spontaneous bacterial peritonitis	226 (1.78)	230 (1.80)	0.985 (0.819, 1.186)	0.876
All cause 5-year hospitalization	2,122 (24.06)	1,835 (20.16)	1.255 (1.169, 1.347)	<0.001
All cause 5-year mortality	1,926 (14.99)	2,055 (15.99)	0.926 (0.866, 0.991)	0.026

gradient (HVPG) measurements or focus narrowly on variceal bleeding [9]. The study by Alamasri *et al.* highlights the clinical relevance and importance of long-term treatment with carvedilol by performing a head-to-head comparison with propranolol in a real-world U.S. population. Importantly, this allows translation of the findings into clinically meaningful outcomes that can be readily assessed by providers at bedside [18].

Why might carvedilol be superior

To understand the greater therapeutic benefit of carvedilol, it is essential to appreciate the underlying pathophysiological mechanisms of portal hypertension in cirrhosis, along with the mechanism of drug action. Portal hypertension in cirrhosis arises from a combination of increased intrahepatic vascular resistance, increased splanchnic blood flow, and the development of a hyper dynamic circulatory state [7,21]. The rise in intrahepatic resistance reflects both structural and dynamic components. Structural changes include architectural distortion from fibrosis and regenerative nodules, while the dynamic component is driven by intrahepatic vasoconstriction and endothelial dysfunction mediated in part by contractile myofibroblasts-activated hepatic stellate cells that express α1-adrenergic receptors [21–24].

Traditional non-selective beta-blockers primarily target the systemic and splanchnic components of portal hypertension. By blocking β1 receptors they reduce cardiac output, and through β2 blockade they promote splanchnic vasoconstriction, thereby lowering portal venous inflow [15,20,25–30]. However, these agents do not directly address the intrahepatic vascular resistance that plays a central role in sustaining portal hypertension.

Carvedilol differs mechanistically in this regard. In addition to β1 and β2 blockade, it also antagonizes α1-adrenergic receptors, producing intrahepatic vasodilation and thereby reducing intrahepatic resistance [15,20]. Because a substantial portion of portal hypertension is driven by this dynamic and potentially reversible component within the hepatic microcirculation, this additional mechanism likely contributes to the greater reductions in hepatic venous pressure gradient (HVPG) observed with carvedilol compared with propranolol in comparative studies [16,17,31].

In the past, other agents aimed at reducing intrahepatic vascular resistance through alpha 1 blockade, such as prazosin and mono-nitrate isosorbide have been evaluated in patients with cirrhosis showing potential benefit. However, they were eventually discontinued due to high rates of systemic hypotension [32–35]. Furthermore, carvedilol has also shown to reduce hepatic fibrosis by promoting apoptosis of HSCs in animal models and has also shown to attenuate angiogenesis dependent liver fibrosis through its anti-angiogenic effect [7].

Taken together, the physiologic data support the central idea behind the findings of Almasri *et al.*: as portal hypertension is the engine driving decompensation, then a drug that lowers portal pressure more effectively should better delay the first clinical decompensation event [18].

The mortality benefit

A noteworthy finding by Almasri *et al.*, although modest, was a significant reduction in all-cause mortality at 5 years, in the carvedilol cohort compared with the propranolol cohort after matching [18].

The first study to provide evidence supporting this beneficial effect of using carvedilol was a competing-risk-meta-analysis by Villanueva *et al*. in 2022. The authors demonstrated that the risk of death was significantly lower in the carvedilol group compared with controls (SHR 0.417; 95% CI 0.194 to 0.896; p = 0.025). This difference remained significant after adjusting for baseline risk factors (SHR 0.417; 95% CI 0.202-0.858; p = 0.017), including Child Pugh class and etiology of cirrhosis [14].

Emerging evidence suggests a possible mortality benefit with carvedilol, although this remains to be confirmed in randomized trials. In 2023, a network-meta-analysis reported that carvedilol ranked highest in reducing both all-cause mortality (68% lower risk) and liver-related mortality (71% lower risk) [36]. Furthermore, a retrospective database study by Mullarkey *et al*., published in 2025, also comparing carvedilol with propranolol in patients with compensated cirrhosis, demonstrated that patients taking carvedilol had a lower hazard of mortality (P = 0.03) compared with those taking cNSSBs [9].

Carvedilol's improved mortality statistics likely stem from its capacity to reduce the incidence of ascites in these patients. Ascites represents the most common complication of cirrhosis [12]. It is reported that the 5-year survival declines from ~80% in compensated cirrhosis to ~30% after the onset of ascites [37]. Controlling portal pressure is fundamental to preventing this complication. Existing literature suggests that effectively reducing portal pressure markedly improves the control of ascites in this cohort of patients [38–41]. Similarly, sustained long-term decrease in portal hypertension is associated with a 50% reduction in developing ascites [12]. Therefore, it is not surprising that carvedilol confers a survival advantage, given its superior hemodynamic response [36]. Consistently, in the study by Almasri *et al.*, the carvedilol cohort had a significantly lower incidence of ascites (8.87% vs. 9.84%, OR=0.893, 95%CI: 0.817–0.976, p=0.012). Additionally, carvedilol has been shown to reduce oxidative stress, decrease the release of inflammatory cytokines, and prevent mitochondrial dysfunction – processes implicated in the progression to decompensated cirrhosis – further contributing to improved mortality [36].

In this context, the study by Almasri *et al.* is very timely, as it adds to the limited but growing body of evidence corroborating the mortality benefit of carvedilol compared to propranolol. Although the reported benefit was marginal, we hypothesize that this may be due to an inherent limitation of the TriNetX database, which cannot differentiate between liver related versus other causes of deaths. Given that deaths in cirrhosis are predominately liver related [14], restricting the analysis to liver-specific deaths might have yielded a more pronounced benefit favoring carvedilol. This rationale is supported by the analysis of Villanueva *et al.* in their meta-analysis, which showed the risk of liver-related death was significantly lower in the carvedilol group than in the control group (SHR 0.320; 95% CI 0.134-0.762; p = 0.010) [14].

Reason for increased hospitalization

An intriguing finding from the study by Almasri *et al.*, was that, despite improvements in mortality, the all cause 5-year hospitalization – both before and after propensity score matching – was significantly higher in the carvedilol group. This may be explained by the drug-related adverse effects outlined below.

Studies in the past have highlighted carvedilol's potential to aggravate systemic hypotension and renal dysfunction [42]. In a meta-analysis by Joshi *et al.*, the carvedilol cohort was associated with a greater reduction in systemic vascular resistance and mean arterial pressure ([MD = –190.55, 95% CI = –307.5 to –73.58; p = 0.001] and [MD = –3.65, 95% CI = –5.94 to –1.36; p = 0.002], (respectively) [43]. In another study, the discontinuation rates for cNSBBs and carvedilol were 6.3% and 9.0%, respectively (p = 0.488). However, common reasons for discontinuation, including hypotension and the necessity to switch beta-blockers did not differ significantly between treatments (p = 0.462) [44].

The concern relates largely to its vasodilator component, which exerts a greater blood pressure lowering effect than cNSSBs. As a result, patients are at risk of developing symptomatic arterial hypotension, or even worsening ascites, secondary to water and sodium retention [7]. These risks are more pronounced at higher doses (e.g., >25 mg/day) than lower doses (e.g., 12.5 mg/day). Cirrhotic patients often exhibit a reduced baseline mean arterial pressure owing to decreased systemic vascular resistance. Further lowering the pressures may increase the likelihood of compromising blood flow to the kidney, leading to complications such as hepato-renal syndrome [43]. A previous meta-analysis also highlighted the increased incidence of side effects in patients treated with carvedilol compared to control. The adverse effects included syncope or collapse, erectile dysfunction in men, and fatigue [45].

Future Direction and Conclusion

In conclusion, the findings presented by Almasri *et al.* [18] further strengthen the mounting evidence favoring carvedilol's first line role in preventing the progression from compensated to decompensated cirrhosis, along with improving mortality. However, clinical decisions must not be drawn from observational studies, but rather from randomized control trials. Notably, no large randomized clinical trial powered for clinical outcomes has directly compared carvedilol with traditional NSBBs. Future research should therefore focus on gaining more insights through a head-to-head comparison using randomized control trials.

Another major limitation to treating patients with clinically significant portal hypertension is early diagnosis, as most remain asymptomatic. HVPG, although being the gold standard, is invasive and clinically impractical. Future research should focus on non-invasive diagnostic tools, such as serological markers and hepatic elastography, to enable earlier detection of CSPH and timely intervention. Finally, whether to stop NSBB treatment in the setting of hepatic decompensation, particularly refractory ascites, is still controversial and is not addressed by current guidelines. Future research should provide more guidance on this topic.

Conflict of Interest

The authors declare no conflicts of interest related to this work.

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Author Contributions

Talha Khalid and Muhammad Ali Butt drafted the manuscript. Raza Malik contributed to manuscript revision and critical review of the intellectual content. All authors approved the final manuscript.

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