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Carvedilol versus Propranolol in Preventing Decompensation in Patients with Compensated Cirrhosis: A Real-World Propensity-Matched Study

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ABSTRACT

Background & Aims: Non-selective beta-blockers are widely used for the management of portal hypertension and prevention of variceal bleeding in patients with liver cirrhosis. While studies have demonstrated carvedilol's superiority in reducing portal pressure compared to propranolol, limited real-world data directly compare their efficacy in preventing decompensation.

Methods: We conducted a retrospective cohort study using the TriNetX database on patients from several healthcare organizations in the US Collaborative Network. Cohorts were defined as adult patients with compensated cirrhosis who were prescribed either carvedilol or propranolol. Propensity score matching was applied to balance demographic, clinical, and laboratory characteristics. The first decompensation event, all-cause hospitalization, and all-cause mortality were defined as outcomes.

Results: After matching, each cohort included 12,890 patients. The mean age was 59.6 years. Comorbidities and laboratory findings were well-balanced between the two groups. Patients receiving carvedilol had a significantly lower risk of developing new decompensating events within five years, including ascites, variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome. Spontaneous bacterial peritonitis was not significantly different between the groups. Post-matching analysis showed marginally reduced all-cause mortality in the carvedilol group at five years.

Conclusions: In this real-world study, carvedilol demonstrated superior efficacy compared with propranolol in reducing key decompensatory events in patients with compensated cirrhosis, likely due to its enhanced ability to lower portal pressure. However, the mortality benefit probably requires further studies to unfold.

Key words: compensated liver cirrhosis – portal hypertension – carvedilol – propranolol.

Abbreviations: AASLD: American Association for the Study of Liver Diseases; BMI: body mass index; CCI: Charlson Comorbidity Index; CSPH: clinically significant portal hypertension; HCO: Healthcare Organization; HRS: hepatorenal syndrome; HVPG: hepatic venous pressure gradient; ICD-10: International Classification of Diseases Tenth Revision; MASH: metabolic dysfunction-associated steatohepatitis; MELD: model for end-stage liver disease; NSBB: non-selective beta-blocker; OR: odds ratio; PSM: propensity score matching; RxNorm: normalized names for clinical drugs; SBP: spontaneous bacterial peritonitis; Std diff.: standardized difference.

INTRODUCTION

Liver cirrhosis can be categorized as 'compensated' or 'decompensated' phases based on several clinical features [1]. A decompensatory phase typically occurs when the portal pressure increases and/or hepatic function deteriorates [2, 3]. These changes result in complications that define the term 'decompensated cirrhosis,' such as ascites, variceal bleeding, and hepatic encephalopathy [1, 4, 5]. It is estimated that the one-year mortality rate is 5.4% in compensated cirrhosis and 20.2% in decompensated cirrhosis [6]. Ascites is the most common first decompensatory condition of cirrhosis. Once ascites develops, a significant decline in both prognosis and quality of life is noted, with an estimated 2-year mortality rate of up to 50% [7].

Portal hypertension is a key driver of multiple decompensation events, resulting from increased intrahepatic resistance, particularly at the level of the hepatic sinusoidal vessels in patients with cirrhosis [4, 8]. Non-selective beta-

blockers (NSBBs) have been important medications in managing patients with portal hypertension, especially in the primary and secondary prevention of variceal hemorrhage [9, 10]. The effectiveness of NSBBs lies in reducing the portal pressure gradient due to decreased cardiac output and splanchnic blood flow through beta-1 and beta-2 blockade, respectively [10]. Propranolol and Nadolol have traditionally been used for this purpose [11-13]. In the past decade, carvedilol has gained favor due to its superior ability to reduce portal pressure compared with other NSBBs. [14]. The PREDESCI trial demonstrated that carvedilol led to a greater reduction in hepatic venous pressure gradient (HVPG) compared to propranolol, even in propranolol non-responders, and also showed a slight (not statistically significant) trend of improved survival [15].

The 2023 American Association for the Study of Liver Diseases (AASLD) guidelines suggest carvedilol as the preferred NSBB for managing portal hypertension due to superior tolerance with potential ascites reduction [16]. Although previous studies have demonstrated the benefits of carvedilol, most were limited by smaller sample sizes, selective patient populations, short follow-up periods, or single-center designs [17]. Large-scale, real-world evidence confirming these findings remains limited. Our study addresses this gap by comparing the effectiveness of carvedilol and propranolol in preventing first decompensation, hospitalizations, and mortality in a large, multi-institutional U.S.-based cohort of patients with compensated cirrhosis, reflecting diverse real-world clinical practice and providing long-term follow-up data.

METHODS

We conducted a retrospective cohort study using the US Collaborative Network within the TriNetX database. TriNetX (Cambridge, MA) is a global federated health research network that combines real-time de-identified electronic health records from multiple healthcare organizations (HCOs) [18]. Clinical variables were identified using International Classification of Diseases, Tenth Revision (ICD-10), procedure codes, and RxNorm medication codes. Quality standards were rigorously applied during query building, matching, and analysis. Data use agreement was mandatory for access, but institutional board review approval was not required since the data were de-identified.

Adult patients (aged ≥ 18 years) diagnosed with compensated cirrhosis, prescribed either carvedilol or propranolol between January 1, 2008, and December 31, 2020, were included in the analysis. Compensated cirrhosis was defined as the diagnosis of 'Fibrosis and Cirrhosis of Liver' which correlates to ICD-10 code of K74 with the exclusion of with any history of decompensating events, including ascites, variceal bleeding, hepatic encephalopathy, jaundice, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), portal vein thrombosis, and hepatopulmonary syndrome (HRS) before the index event (NSBBs initiation date). This approach was intended to focus the analysis on the impact of NSBBs on the first presentation with a decompensation event. Patients with a diagnosis of hepatocellular carcinoma or a history of liver transplantation before the index event were excluded from the study cohort.

Two cohorts were created, one for patients taking carvedilol (RxNorm 20352) and the other for patients taking propranolol (RxNorm 8787). One-to-one propensity score matching (PSM) was performed to balance the demographic, comorbidities, and laboratory characteristics of the two groups. Demographic variables included age at index event, sex (male or female), race (White, Black or African American, Asian), ethnicity (Hispanic or Latino), and body mass index (BMI). Baseline comorbidities included hypertension and others that were selected based on the Charlson Comorbidity Index (CCI), a validated tool to adjust for comorbidities in observational studies [19]. This included 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. While Model for End-Stage Liver Disease (MELD) scores were not directly available in TriNetX, we included MELD score components (creatinine, bilirubin, INR) and additional laboratory markers (platelet count, albumin, AST, ALT, sodium, hemoglobin) in the propensity score matching to account for liver disease severity. Laboratory values were selected automatically by the TriNetX platform as the mean of the last reported result before the index event. PSM in TriNetX employs a greedy nearest-neighbor algorithm with a caliper width of 0.1 pooled standard deviations and randomizes the order of rows. A standardized difference (Std diff.) of less than 0.1 was used as a criterion for successful matching in each category.

Outcome Definitions and Time Window

Liver cirrhosis first decompensation events were defined based on corresponding ICD-10 codes. These outcomes included ascites, variceal bleeding, and hepatic encephalopathy at one year and five years from the index event. We also included five-year hepatorenal syndrome and spontaneous bacterial peritonitis. Although SBP and HRS typically occur after the development of ascites and are considered further decompensating events, they can be the first clinically recognized or documented manifestation of decompensation in some patients. This inclusive definition was chosen to reflect real-world presentation and the nature of coding practices in administrative databases. 5-year all-cause hospitalization and all-cause mortality were also included as outcomes.

We also conducted five-year outcome analyses on the raw (unmatched) cohorts to provide a complementary perspective and reduce the potential bias introduced by PSM. Statistical analysis was conducted using the built-in statistical analysis environment within TriNetX. PSM was performed within the TriNetX software. 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.

RESULTS

70 HCOs were queried in the US Collaborative Network, and 70 HCOs responded. The query resulted in 44,111 patients with compensated cirrhosis taking either carvedilol or propranolol. Of them, 28,831 patients were included in

the carvedilol group and 15,280 in the propranolol group. Before matching, the distribution of underlying liver disease etiologies was as follows: metabolic dysfunction-associated steatohepatitis accounted for 19% in both the carvedilol and propranolol groups. Alcohol-related liver disease was more common in the propranolol group (31%) compared to the carvedilol group (21%). Chronic viral hepatitis was present in 27% of patients in both groups, while autoimmune hepatitis accounted for 3% in each group. The remaining patients had unidentified etiologies.

Before matching, the carvedilol group had a notably higher burden of cardiovascular comorbidities compared to the propranolol group. Specifically, 45.6% of patients on carvedilol had hypertension versus 29.7% on propranolol, 33.1% had diabetes compared to 20.2%, and ischemic heart disease was present in 19.5% versus only 5.6%. Heart failure was also more common in the carvedilol group at 22.5%, compared to 5.0% in propranolol users ($p < 0.001$). Other vascular conditions, such as cerebrovascular disease (8.2% vs. 4.3%) and peripheral vascular disease (4.7% vs. 1.6%), followed the same trend, all with significant differences. Baseline characteristics before PSM are outlined in Table I. After matching, 12,890 patients were included in each group, with a mean age being 59.6 ± 12.0 years in both groups, and females comprised 43.0% and 42.4% of the carvedilol group and propranolol group, respectively. The most common race was white, 67.8% and 67.1% in the carvedilol and propranolol cohorts, respectively. Baseline characteristics after PSM are outlined in Table II.

Table I. Characteristics of cohorts before propensity score matching

Variable*	Carvedilol (N = 28,831)	Propranolol (N = 15,280)	p	Std diff.
Age at index event** (mean ± SD)	63.1 ± 11.7	57.4 ± 13.1	<0.001	0.458
Gender, n (%)				
Male	15,000 (52.2%)	7,168 (47.7)	<0.001	0.090
Female	10,834 (37.7%)	6,676 (44.4)	<0.001	0.137
Body mass index				
Body mass index (mean ± SD)	30.9 ± 7.8	30.3 ± 7.7	<0.001	0.069
Race/Ethnicity				
White	16,481 (57.3)	10,300 (68.5)	<0.001	0.232
Black or African American	5,841 (20.3)	1,273 (8.5)	<0.001	0.343
Hispanic or Latino	2,345 (8.2)	1,794 (11.9)	<0.001	0.126
Asian	847 (2.9)	381 (2.5)	0.013	0.025
Comorbidities, n (%)				
Hypertension	13,117 (45.6)	4,465 (29.7)	<0.001	0.333
Diabetes mellitus	9,527 (33.1)	3,034 (20.2)	<0.001	0.296
Ischemic heart disease	5,621 (19.5)	837 (5.6)	<0.001	0.432
Heart failure	6,457 (22.5)	746 (5.0)	<0.001	0.526
Cerebrovascular disease	2,368 (8.2)	640 (4.3)	<0.001	0.165
Chronic kidney disease	5,711 (19.9)	876 (5.8)	<0.001	0.429
Peripheral vascular disease	1,352 (4.7)	240 (1.6)	<0.001	0.179
Dementia	364 (1.3)	145 (1.0)	0.005	0.029
COPD	3,114 (10.8)	902 (6.0)	<0.001	0.175
HIV	414 (1.4)	207 (1.4)	0.592	0.005
Laboratory values (mean)				
Sodium (mmol/L)	138.1	138.1	0.398	0.012
Creatinine (mg/dL)	1.6	1.0	<0.001	0.349
INR	1.3	1.3	<0.001	0.076
Albumin (g/dL)	3.5	3.5	0.933	0.001
Bilirubin (mg/dL)	1.0	1.4	<0.001	0.202
ALT (U/L)	41.1	44.7	0.002	0.047
AST (U/L)	50.0	58.7	<0.001	0.081
Platelets (10^3/uL)	179.0	158.6	<0.001	0.215
Hemoglobin (g/dL)	11.8	12.1	<0.001	0.128

*Values are based on available data; ** Index event: carvedilol or propranolol initiation date; Std Diff: standardized difference; SD: standard deviation; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus disease; INR: international normalized ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table II. Characteristics of cohorts after propensity score matching

Variable*	Carvedilol (N=12,890)	Propranolol (N=12,890)	p	Std diff
Age at index event** (mean ± SD)	59.6 ± 12.0	59.6 ± 12.0	0.867	0.002
Gender, n (%)				
Male	6,262 (48.6)	6,318 (49.0)	0.485	0.009
Female	5,549 (43.0)	5,463 (42.4)	0.279	0.013
Body mass index				
Body mass index (mean ± SD)	31.2 ± 7.8	30.3 ± 7.6	<0.001	0.114
Race/Ethnicity, n (%)				
White	8,739 (67.8)	8,650 (67.1)	0.237	0.015
Black or African American	1,160 (9.0)	1,257 (9.8)	0.038	0.026
Hispanic or Latino	1,396 (10.8)	1,357 (10.5)	0.432	0.010
Asian	319 (2.5)	346 (2.7)	0.289	0.013
Comorbidities				
Hypertension	4,182 (32.4)	4,125 (32.0)	0.447	0.009
Diabetes mellitus	2,815 (21.8)	2,791 (21.7)	0.717	0.005
Ischemic heart disease	853 (6.6)	836 (6.5)	0.669	0.005
Heart failure	835 (6.5)	745 (5.8)	0.019	0.029
Cerebrovascular disease	574 (4.5)	580 (4.5)	0.857	0.002
Chronic kidney disease	892 (6.9)	865 (6.7)	0.505	0.008
Peripheral vascular disease	235 (1.8)	231 (1.8)	0.852	0.002
Dementia	118 (0.9)	125 (1.0)	0.652	0.006
COPD	845 (6.6)	809 (6.3)	0.360	0.011
HIV	142 (1.1)	163 (1.3)	0.226	0.015
Laboratory values (mean)				
Sodium (mmol/L)	138.1	138.2	0.733	0.006
Creatinine (mg/dL)	1.1	1.0	0.011	0.046
INR	1.3	1.3	0.161	0.032
Albumin (g/dL)	3.6	3.6	0.265	0.021
Bilirubin (mg/dL)	1.2	1.3	0.033	0.040
ALT (U/L)	45.7	42.5	0.015	0.045
AST (U/L)	55.8	55.4	0.810	0.004
Platelets (10^3/uL)	160.5	161.3	0.638	0.009
Hemoglobin (g/dL)	12.1	12.1	0.749	0.006

For abbreviations see Table I.

At one-year, hepatic encephalopathy occurred significantly less often in the carvedilol group compared with the propranolol group (4.16% vs. 4.96%; OR=0.831, 95%CI: 0.735–0.940, p=0.003). The 1-year incidence of ascites was not statistically significant between groups (3.83% vs. 4.18%; OR=0.913, 95%CI: 0.800–1.042, p=0.178) as well as variceal bleeding (0.83% vs. 0.77%; OR=1.078, 95%CI: 0.818–1.421, p=0.594). Table III.

Five-year Outcomes Before Propensity Score Matching

Before PSM, carvedilol was associated with a significantly lower incidence of multiple decompensation events compared to propranolol. Specifically, rates of ascites (7.61% vs. 9.96%; OR=0.745, 95%CI: 0.692–0.801, p<0.001), variceal bleeding (1.18% vs. 2.26%; OR=0.519, 95%CI: 0.445–0.605, p<0.001), hepatic encephalopathy (7.35% vs. 10.46%; OR 0.679, 95% CI 0.632–0.730, p<0.001), and HRS (0.77% vs. 1.29%; OR 0.588,

Table III. One-year first decompensation events by comparing carvedilol and propranolol cohorts after matching

Outcome*	Carvedilol n (%)	Propranolol n (%)	Odds ratio (95% CI)	p
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)	574 (4.96)	0.831 (0.735, 0.940)	0.003

* Values are based on available data.

95% CI 0.484–0.714, p<0.001) were all significantly lower in the carvedilol group. There was no significant difference in SBP (1.71% vs. 1.74%; OR=0.984, 95%CI: 0.845–1.146, p=0.838). However, patients in the carvedilol cohort experienced higher rates of all-cause 5-year hospitalizations (26.56% vs. 19.91%; OR=1.455, 95%CI: 1.372–1.542, p<0.001) and all-cause 5-year mortality (19.29% vs. 15.10%; OR=1.344, 95%CI: 1.274–1.418, p<0.001). (Table III and Fig. 1).

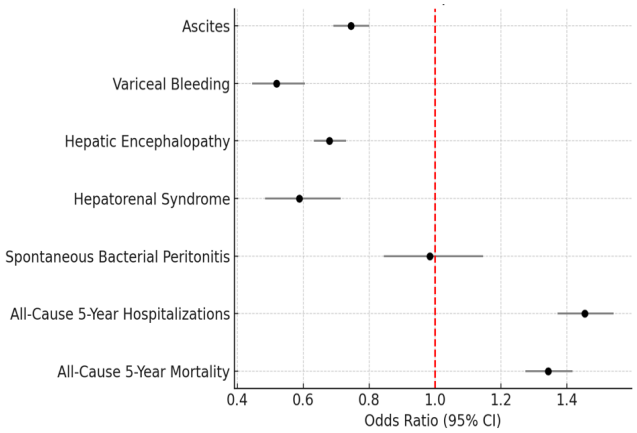

Fig. 1. Five-year outcomes by comparing carvedilol and propranolol cohorts before matching.

Five-year Outcomes after Propensity Score Matching

After PSM, carvedilol group again had a significantly lower incidence of ascites (8.87% vs. 9.84%, OR=0.893, 95%CI: 0.817–0.976, p=0.012), variceal bleeding (1.71% vs. 2.16%, OR=0.788, 95%CI: 0.658–0.944, p=0.010), hepatic encephalopathy (8.80% vs. 10.53%, OR=0.819, 95%CI: 0.751–0.894, p<0.001), and HRS (0.95% vs. 1.36%, OR=0.694, 95%CI: 0.550–0.876, p=0.002), compared to propranolol. There was no significant difference in the rate of SBP (1.78% vs. 1.80%, OR=0.985, 95%CI: 0.819–1.186, p=0.876). All-cause 5-year hospitalizations were more frequent in the carvedilol group (24.06% vs. 20.16%, OR=1.255, 95%CI: 1.169–1.347, p<0.001). However, all-cause 5-year mortality was slightly lower in the carvedilol group (14.99% vs. 15.99%, OR=0.926, 95%CI: 0.866–0.991, p=0.026). (Table IV and Fig. 2).

DISCUSSION

This retrospective analysis of a large, propensity-score matched real-world cohort from a multi-center database

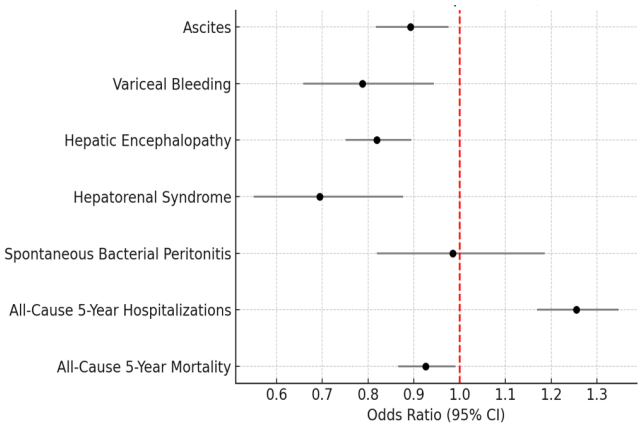

Fig. 2. Five-year outcomes by comparing carvedilol and propranolol cohorts after matching

found that carvedilol was more effective than propranolol in preventing new decompensation events, such as ascites, variceal bleeding, hepatic encephalopathy, and HRS over five years. No significant difference was observed in the incidence of SBP between the groups. While the carvedilol cohort experienced a higher rate of hospitalizations, it also showed a marginal reduction in all-cause mortality at five years in the post-matching analysis.

These findings align with previous studies that have demonstrated the superiority of carvedilol [20]. In the PREDESCI trial, patients with compensated cirrhosis and clinically significant portal hypertension (CSPH) were evaluated by intravenous propranolol to assess the acute hemodynamic response. Non-responders were subsequently given carvedilol, and this group showed better hemodynamic response compared to the propranolol group at one and two years [15]. Additionally, the overall decompensation, primarily due to the occurrence of ascites, was less prevalent in the beta-blocker group compared to the placebo group, with the primary benefit being more prominent when the treatment duration exceeded two years [15]. These findings were supported by a systematic review and meta-analysis conducted by Sinagra et al. [14]. Our analysis revealed a significant difference in preventing new ascites, variceal bleeding, hepatic encephalopathy, and HRS at five years, favoring carvedilol, with this effect being persistent before and after matching for a wide range of confounding variables. This highlights

Table IV. Five-year outcomes by comparing carvedilol and propranolol cohorts before matching

Outcome*	Carvedilol n (%)	Propranolol n (%)	Odds ratio (95% CI)	p
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 hospitalizations	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

* Values are based on available data.

Table V. Five-year outcomes by comparing carvedilol and propranolol cohorts after matching

Outcome*	Carvedilol n (%)	Propranolol n (%)	Odds ratio (95% CI)	p
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 hospitalizations	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

* Values are based on available data.

the clinical relevance of these results and the importance of long-term treatment with carvedilol in patients with compensated cirrhosis. Our findings complement prior studies by confirming carvedilol's superiority in a broad, real-world U.S. population. Unlike prior studies with narrow inclusion criteria, our analysis demonstrates that carvedilol's protective effect against decompensation persists across diverse patient populations and over a longer follow-up period, highlighting its relevance for routine clinical practice.

The dual mechanism of carvedilol, which blocks both beta and alpha receptors, enables it to be more effective than traditional NSBB (such as propranolol and nadolol), even at low doses (6.25–12.5 mg per day) [10]. However, at higher doses (>25 mg daily), carvedilol can cause a significant reduction in the mean arterial pressure, which might in turn increase some adverse events such as hospitalizations [14]. Switching from propranolol to carvedilol may be considered in patients without response or intolerance to propranolol. However the evidence supporting the universal transition of patients with compensated cirrhosis remains inconclusive [16, 21]. Kalambokis et al. [22] described a significant improvement in glomerular filtration rate and renal perfusion at 12-month follow-up when patients were switched from propranolol (given for variceal bleeding prophylaxis) to carvedilol. This was accompanied by a significant reduction of plasma renin activity and serum noradrenaline as well [22]. These findings correlate with the hypothesis that targeting hyperdynamic portal hypertensive circulation is the key to preventing decompensation [23].

Fortea et al. [17] published a multicenter retrospective European study involving 540 patients with compensated and decompensated cirrhosis who underwent hemodynamic variable pressure gradient measurements. The study found that compared to propranolol and nadolol, carvedilol significantly reduced the risk of first decompensation without compromising safety. The findings of our study align with this conclusion when considered in aggregate.

Our study did not differentiate mortality due to liver-related causes versus other etiologies, reflecting an inherent limitation of the TriNetX database. Before matching, the carvedilol group had an expected higher burden of cardiovascular comorbidities, likely contributing to their initially higher mortality compared to the propranolol group. Propensity score matching for demographics, comorbidities, and estimated liver disease severity using key laboratory markers helped minimize confounding and reduce selection bias. After matching, all-cause mortality was slightly lower and statistically significant in the carvedilol group; however, the clinical significance of this difference should be interpreted with caution, given the unspecified cause of death.

The hospitalization rate has been infrequently addressed in prior studies comparing carvedilol and propranolol. In addition, patients with cirrhosis may be hospitalized due to decompensation or other complications that are more common in this population, such as bacterial infections beyond SBP [24, 25]. Our analysis showed a higher all-cause hospitalization rate in the carvedilol group over five years, both before and after matching. Although the database does not capture reasons for hospitalization, this may relate to carvedilol's pharmacologic effects such as hypotension or bradycardia or to the higher cardiovascular disease burden in this group.

Our study has limitations, including its retrospective nature of the study. In addition, although we used propensity score matching to reduce bias, some residual confounding may remain due to variables not consistently captured in the dataset, such as alcohol cessation, sustained virologic response in hepatitis C, medication adherence, and the severity of portal hypertension. These factors could still influence outcomes and should be kept in mind when interpreting our findings. Also, we were unable to adjust for potential differences in treatment era between carvedilol and propranolol users.

TriNetX does not capture certain patient-level factors that may influence outcomes, including alcohol abstinence, hepatitis C sustained virologic response (SVR), dosing, indication or adherence to prescribed medications. These unmeasured variables may contribute to residual confounding.

Furthermore, the use of the diagnosis code for "fibrosis and cirrhosis of the liver" may have included patients with hepatic fibrosis alone and not exclusively those with cirrhosis. This can affect the generalizability of the study due to possible heterogeneity in the included cohorts. As with most administrative database studies, reliance on the ICD-10 code 'fibrosis and cirrhosis of the liver' may have included patients with advanced fibrosis without confirmed cirrhosis. This limitation is inherent and unlikely to be fully avoidable in database analyses and may slightly underestimate or overestimate the effect of carvedilol. Another limitation of this study is the potential for missing or incomplete data within the TriNetX platform. TriNetX does not impute missing values and retains data as received from participating institutions. Therefore, gaps in electronic health records may exist and cannot be quantified or adjusted for. Also, because the TriNetX network is predominantly composed of

U.S.-based healthcare organizations, the generalizability of our findings to non–U.S. populations may be limited.

Despite these limitations, this study represents one of the most comprehensive analyses of real-world data to compare carvedilol and propranolol in patients with compensated cirrhosis.

CONCLUSIONS

In this propensity score-matched retrospective study, carvedilol demonstrated significant benefits in preventing decompensation compared to propranolol in patients with compensated cirrhosis. Although a clear all-cause mortality benefit with carvedilol remains uncertain, these findings provide valuable insights to guide future investigations.

Conflicts of interest: None to declare.

Authors' contribution: H.A. and N.M.U.D. conceived and designed the study. H.A. collected the data. M.A.B, R.H., G.S., H.K. and N.M.U.D. analysed the data. H.A., G.S. and H.K. drafted the manuscript. H.A., J.T.B., R.M., M.V.L and N.M.U.D. revised the manuscript for important intellectual content. R.K., J.T.B., R.M., M.V.L supervised the study. All the authors read and approved the final version of the manuscript.

REFERENCES

1. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74:1014-1048. doi:10.1002/hep.31884
2. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74:1014-1048. doi:10.1002/hep.31884
3. D'Amico G, Bernardi M, Angeli P. Towards a new definition of decompensated cirrhosis. J Hepatol 2022;76:202–207. doi:10.1016/j.jhep.2021.06.018
4. Berzigotti A. Advances and challenges in cirrhosis and portal hypertension. BMC Med 2017;15:200. doi:10.1186/s12916-017-0966-6
5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol 2006;44:217–231. doi:10.1016/j.jhep.2005.10.013
6. Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver Int 2012;32:1407–1414. doi:10.1111/j.1478-3231.2012.02830.x
7. Perri GA. Ascites in patients with cirrhosis. Can Fam Physician 2013;59:1297–1299.
8. Iwakiri Y. Pathophysiology of Portal Hypertension. Clin Liver Dis 2014;18:281–291. doi:10.1016/j.cld.2013.12.001
9. Garcia-Tsao G, Bosch J. Management of Varices and Variceal Hemorrhage in Cirrhosis. N Engl J Med 2010;362:823–832. doi:10.1056/NEJMra0901512
10. Rodrigues SG, Mendoza YP, Bosch J. Beta-blockers in cirrhosis: Evidence-based indications and limitations. JHEP Rep 2020;2:100063. doi:10.1016/j.jhepr.2019.12.001
11. Bosch J. Carvedilol as Best β-Blocker for Secondary Prophylaxis of Variceal Bleeding: Are We There, or Not Yet? Clin Gastroenterol Hepatol 2023;21:2195–2196. doi:10.1016/j.cgh.2022.08.026
12. Elfeki MA, Singal AK, Kamath PS. Pharmacotherapies for Portal Hypertension: Current Status and Expanding Indications. Curr Hepatol Rep. 2023;22:44–50.
13. Abid S, Ali S, Baig MA, Waheed AA. Is it time to replace propranolol with carvedilol for portal hypertension? World J Gastrointest Endosc. 2015 May 16;7(5):532–9. doi:10.1007/s11901-023-00600-z
14. Sinagra E, Perricone G, D'Amico M, Tinè F, D'Amico G. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. Aliment Pharmacol Ther 2014;39:557–568. doi:10.1111/apt.12634
15. Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2019;393:1597–1608. doi:10.1016/S0140-6736(18)31875-0
16. Kaplan DE, Ripoll C, Thiele M, et al. AASLD Practice Guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology 2024;79:1180-1211. doi:10.1097/HEP.0000000000000647
17. Fortea JI, Alvarado-Tapias E, Simbrunner B, et al. Carvedilol *vs.* propranolol for the prevention of decompensation and mortality in patients with compensated and decompensated cirrhosis. J Hepatol 2025;80:70-80. doi:10.1016/j.jhep.2024.12.017
18. Palchuk MB, London JW, Perez-Rey D, et al. A global federated real-world data and analytics platform for research. JAMIA Open 2023;6:ooad035. doi:10.1093/jamiaopen/ooad035
19. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. Psychother Psychosom 2022;91:8-35. doi:10.1159/000521288
20. Christaki M, Biros D, Tsiakas I, Milionis H, Kalambokis GN. Carvedilol is superior to propranolol in preventing first and further decompensation, and mortality in patients with cirrhosis. J Hepatol 2025;83:e172-e174. doi:10.1016/j.jhep.2025.04.032
21. Serper M, Kaplan DE, Taddei TH, Tapper EB, Cohen JB, Mahmud N. Nonselective beta blockers, hepatic decompensation, and mortality in cirrhosis: A national cohort study. Hepatology 2023;77:489-500. doi:10.1002/hep.32737
22. Kalambokis GN, Christaki M, Tsiakas I, et al. Conversion of Propranolol to Carvedilol Improves Renal Perfusion and Outcome in Patients With Cirrhosis and Ascites. J Clin Gastroenterol 2021;55:721-729. doi:10.1097/MCG.0000000000001431
23. Ortiz GA, Garcia-Tsao G. Future Pharmacological Therapies of Portal Hypertension. Curr Hepatol Rep 2019;18:36–48. doi:10.1007/s11901-019-00448-2
24. Garg SK, Goyal H, Obaitan I, et al. Incidence and predictors of 30-day hospital readmissions for liver cirrhosis: insights from the United States National Readmissions Database. Ann Transl Med 2021;9:1052–1052. doi:10.21037/atm-20-1762
25. Tapper EB, Halbert B, Mellinger J. Rates of and Reasons for Hospital Readmissions in Patients With Cirrhosis: A Multistate Population-based Cohort Study. Clin Gastroenterol Hepatol 2016;14:1181-1188. e2. doi:10.1016/j.cgh.2016.04.009