Beta-Blockers Lower First Decompensation in Patients With Cirrhosis and Enduring Portal Hypertension After Etiological Treatment

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BACKGROUND AND AIMS: **Non-selective beta-blockers (NSBBs) can lower the risk of first decompensation in patients with cirrhosis and clinically significant portal hypertension (CSPH) (identified by a hepatic venous pressure gradient ≥10 mm Hg) with active etiology. Our aim was to examine the effect of NSBBs on first decompensation occurrence in patients with cirrhosis and enduring CSPH after etiological treatment.**

METHODS: **Patients with compensated cirrhosis and clinical evidence of CSPH (gastroesophageal varices [GEVs] and/or spontaneous portosystemic collaterals [SPSSs]) after 2 years from etiological treatment. The primary endpoint was first decompensation (occurrence of variceal bleeding, ascites, or hepatic encephalopathy) in patients on NSBBs vs off NSBBs.**

RESULTS: **The final cohort included 406 patients. Baseline characteristics of patients on NSBBs (n = 187) and off NSBBs (n = 219) were comparable, except for signs of portal hypertension that were more pronounced in the on-NSBBs group. During a mean follow-up of 32 months, 127 (31%) patients decompensated, with ascites being the most common (77%) decompensating event. Decompensation rates were lower in patients on NSBBs (16% vs 44%; $P < .0001$). The benefit of NSBBs on decompensation was maintained in patients with small GEVs (17% vs 43%; $P < .0001$), in those with spontaneous portosystemic shunt only (8% vs 43%; $P = .003$), and in each different etiology, including hepatitis C virus–cured cirrhosis (9% vs 32%; $P < .0001$). At Cox regression analysis, hemoglobin, Child-Pugh, Model for End-Stage Liver Disease–Sodium, diabetes at baseline, and previous bacterial infections were independent predictors of decompensation, while NSBBs use had a protective effect (hazard ratio, 0.32; 95% confidence interval, 0.20–0.49; P < .0001). NSBBs use significantly reduced bacterial infection rates (hazard ratio, 0.36; 95% confidence interval, 0.22–0.58; $P < .0001$).**

CONCLUSION: **NSBBs decrease the risk of first decompensation in patients with cirrhosis and enduring CSPH after etiological treatment.**

Keywords: Nonselective Beta-Blockers; Ascites; Hepatic Decompensation; Carvedilol.

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Abbreviations used in this paper: CI, confidence interval; CSPH, clinically significant portal hypertension; DAA, direct-acting antiviral; EVL, endoscopic variceal ligation; GEV, gastroesophageal varix; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; HVPG, hepatic venous pressure gradient; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; NSBB, nonselective beta-blocker; PH, portal hypertension; PVT, portal vein thrombosis; SPSS, spontaneous portosystemic shunt.

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Portal hypertension (PH) is the main driver of the transition from compensated to decompensated cirrhosis, 2 entities with different symptoms and mortality rates.[1] Decompensation, according to the last Baveno consensus,[2] is defined by the occurrence of ascites, variceal bleeding and/or hepatic encephalopathy (HE).

When the portal pressure gradient (indirectly measured as hepatic venous pressure gradient [HVPG]) is ≥10 mm Hg, clinical decompensation might develop.[2] This state is identified as clinically significant portal hypertension (CSPH), as patients progressing to decompensation have a higher risk of death.[1] The identification of CSPH by HVPG has been mostly validated in patients with alcohol-related and active-viral cirrhosis, while concerns exist in patients with other etiologies.[3]

In the last 4 decades, non-selective beta-blockers (NSBBs) have been the cornerstone of therapy for primary and secondary prophylaxis of variceal bleeding.[4] Subsequent evidence broadened the target population to all patients with cirrhosis and CSPH,[5] as their use can mitigate the development of any decompensating event.[6] The landmark study by Villanueva et al,[6] demonstrating the benefit of NSBBs in preventing any decompensating event, was carried out in patients with compensated cirrhosis and CSPH (selected by HVPG ≥10 mm Hg) before the era of direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV).

Concerns were subsequently raised[7] whether (1) the NSBB benefit also applies to patients with clinical evidence of CSPH (presence of gastroesophageal varices [GEVs] of any size and/or spontaneous portosystemic collaterals [spontaneous portosystemic shunt (SPSS)]) without HVPG measurement and (2) NSBB treatment remains beneficial in patients whose etiological factor has been removed/under control. In patients with cirrhosis and CSPH, HCV treatment is able, in fact, to reduce HVPG for up to 2 years post-treatment.[8] However, even in this cohort,[8] 53%–65% of patients experienced persistent CSPH after 2 years from DAA treatment, remaining at risk of decompensation.

The main aim of our study was to examine the effect of NSBBs on first decompensation in patients with cirrhosis and clinical evidence of persistent CSPH after 2 years following etiological treatment.

What You Need to Know

Background

Nonselective beta-blockers (NSBBs) lower first decompensation occurrence in patients with cirrhosis and clinically significant portal hypertension (CSPH) with active etiology, but their efficacy in patients with treated etiology has been questioned.

Findings

In patients with clinical evidence of CSPH after 2 years of etiological treatment, NSBBs lower the occurrence of first decompensation (mainly ascites). The benefit is maintained in each different etiology, including hepatitis C virus–cured cirrhosis.

Implications for patient care

Selecting patients according to the clinical signs CSPH, NSBBs can be offered also in centers in which hepatic venous pressure gradient or liver stiffness measurement are not available.

Patients and Methods

Study Population

This was a monocentric observational study of consecutive patients with compensated cirrhosis without previous decompensation with clinical evidence of CSPH after 2 years following etiological treatment, evaluated at our Liver Unit between 2017 and 2020 (Supplementary Figure 1).

Diagnosis of cirrhosis was based on clinical, biochemical, imaging, and/or histological criteria (all metabolic dysfunction–associated steatotic liver disease [MASLD]–related cirrhosis were histologically confirmed), and clinical evidence of CSPH was defined as the presence of GEVs at upper gastrointestinal endoscopy and/or SPSS at cross-sectional imaging. To minimize the potential long-term impact of etiological treatment on PH,[8] we used the time frame of 2017–2020 for patient enrollment because in our center the majority of patients with HCV-related cirrhosis underwent DAA treatment between 2015 and 2018. Thus, by 2017–2020. patients were expected to be enrolled in this study 2 years post–etiological treatment. We applied identical selection criteria to all patients of different etiologies: patients with hepatitis B virus (HBV) cirrhosis were all on a nucleos(t)ide analogue and included after 2 years from first undetectable HBV-DNA; patients with alcohol-related cirrhosis had proved abstinence for 2 years prior their inclusion; and patients with autoimmune cirrhosis had 2 years of stable remission under specific treatment.

For patients with MASLD-related cirrhosis, definitive etiological treatment was still lacking. We chose not to exclude these patients in order to give an updated overview of the benefit of NSBBs in a modern population, as the use of NSBBs has been questioned in both groups of patients (those with treated etiology and those with MASLD-related cirrhosis). Patients with MASLD received treatment for diabetes,

hypercholesterolemia, and/or arterial hypertension as clinically indicated. They were included in this study 2 years after starting these treatments to align them as closely as possible with the other patients.

Exclusion criteria were age <18 or >80 years, no GEVs or SPSS, previous transjugular intrahepatic portosystemic shunt, splenectomy, previous hepatic decompensation, active (ie, not yet treated with locoregional therapy) hepatocellular carcinoma (HCC), HCC beyond Milan criteria, diagnosis of vascular liver disease at histology, heart failure, hepatopulmonary syndrome, portopulmonary hypertension, expected survival lower than 6 months, and neurologic/psychiatric disorders hampering HE assessment. Patients with complete portal vein thrombosis (PVT) or partial PVT under anticoagulant therapy were also excluded, as anticoagulation may have a direct impact on decompensation.[9]

Inclusion date was the first visit occurring 2 years (±1 month) following etiological treatment.

Patient Evaluation

Data on etiology of cirrhosis, comorbidities, and adherence to pharmacological treatment were collected at enrollment and throughout the follow-up (Supplementary Materials).

Routine laboratory tests were conducted at enrollment to calculate prognostic scores. Ultrasound for HCC surveillance and PVT assessment was performed at 6-month intervals, or sooner if clinically indicated, as routine clinical practice.

Abdominal computed tomography scans were reassessed by expert radiologists in hepatic diseases. SPSSs were defined as spontaneous communications between the spleno-mesenteric-portal axis and the systemic venous system, excluding GEVs, and SPSSs were classified according to the site of connection (Supplementary Materials).[10]

Upper gastrointestinal endoscopy was performed in all patients with cirrhosis regardless the noninvasive criteria to avoid endoscopy,[11] and GEVs, when present, were classified as small or medium-large with or without red wale marks.[12]

NSBBs Use

The first evidence on the benefit of NSBBs to prevent any decompensating event in patients with cirrhosis and CSPH became available in 2017.[13] Since then, in our center, NSBBs treatment has been initiated in some patients based on the clinical evidence of CSPH, even in cases in which only small GEVs or SPSS only (without GEV) were present. The proposal to initiate NSBBs treatment was clinician dependent considering the clinical/hemodynamic characteristics of the patient and the potential contraindications. The first choice for primary prophylaxis of variceal bleeding in patients with medium-large GEV was NSBBs, while endoscopic variceal ligation (EVL) was performed in those patients intolerant/with contraindications to NSBBs. Only patients starting NSBBs after 2 years from etiological treatment were included in this study (Supplementary Figure 1). All the patients were, therefore, naïve to NSBBs treatment.

NSBBs were titrated to the maximum tolerated dose, up to 120 mg/d for propranolol and 12.5/d for carvedilol. A few patients were taking higher doses of carvedilol for concomitant cardiological reasons, mainly arterial hypertension.

All patients, on-NSBBs or off-NSBBs, maintained the same treatment state until the end of follow-up. No patient was switched from one group to another.

Outcomes and Follow-Up

The primary endpoint was the occurrence of first hepatic decompensation, defined as the development of variceal bleeding, ascites, or overt HE (Supplementary Materials)[2] in patients on-NSBBs vs those off-NSBBs.

During follow-up, ultrasound surveillance was conducted every 6 months (or sooner) in accordance with the international guidelines, and HCC and/or PVT development was confirmed by computed tomography scan.

Complications like acute kidney injury, hepatorenal syndrome, and bacterial infections were also recorded. Bacterial infections were diagnosed and treated according to the international and local guidelines (Supplementary Materials). In order to explore the relationship between bacterial infections and first decompensation, only bacterial infections occurring before decompensation were considered. Therefore, episodes of spontaneous bacterial peritonitis, that by definition require the presence of ascites, were not included.

In order to reduce reverse causality, we considered a 6-month lag after baseline to start our follow-up, so the accrual of person years at risk starts 6 months after inclusion.

The end of follow-up was June 2023. For those patients that experienced decompensation, the follow-up was stopped the day of first decompensation. Because PVT and/or HCC occurrence (and their relative treatment) might have an impact on decompensation independently from NSBBs, they were considered as competing risk events and follow-up stopped (patient censored as compensated) at the time of their diagnosis.

Ethical Approval

The study was conducted in accordance with the Helsinki Declaration principles and approved by our institutional review boards (MITIGO study-405/2023). Informed consent was obtained from participants still alive/on follow-up and waived for dropouts.

Statistical Analysis

Continuous variables were evaluated for homogeneity by Levene's test, expressed as mean ± SD, and compared using Student *t* test. Categorical parameters were reported as frequency and compared by chi-square test. Cumulative incidence of decompensation was estimated considering PVT and HCC as competing events and curves compared by Gray's test. Predictors of decompensation and of bacterial infections were identified by Cox regression analysis with stepwise backward selection method, reporting hazard ratio (HR) and 95% confidence interval (CI) for each predictor. Receiver-operating characteristic curve analysis was performed for continuous parameters of interest. Values of $P < .05$ were considered statistically significant. Statistical analysis was performed using IBM-SPSS (version 27) and R software (R Foundation for Statistical Computing, R version 4.2.3), cmprsk-package (https://cran.r-project.org/web/packages/cmprsk/index.html).

Results

A total of 406 patients were included in the final analysis (Supplementary Figure 1). Baseline characteristics are outlined in Table 1. The mean age for the entire cohort was 61 years, and 262 (64.5%) patients were men. The main etiology of cirrhosis was viral (59%), followed by alcohol (14%). The majority of patients were Child-Pugh A (85%), with the rest being all Child-Pugh B7. Diabetes at baseline was present in 34% of patients, all of them under specific treatment. History of HCC was found in 4% of patients and PVT in 3%.

The majority of patients (n = 299 [74%]) had GEVs, 206 of them having small GEVs (51% of the entire cohort), none of them associated with red wale marks. A total of 281 (69%) patients had SPSSs, and the majority of them (58%) had paraumbilical vein recanalization (Supplementary Table 1). A total of 107 (26%) patients had SPSS only, showing no GEVs.

A total of 187 (46%) patients were on NSBBs, the majority (77%) on propranolol with a median dose of 62 mg/d. The 2 groups (on-NSBBs and off-NSBBs) had comparable baseline characteristics (Table 1) regarding etiology of liver disease, comorbidities, blood tests, and relative liver function. Patients on NSBBs had a significantly lower mean platelet count and higher rate of GEVs.

Outcomes

In a mean time of 32 ± 22 months, 127 (31%) patients decompensated: 98 (24%) developed ascites (77% of all the decompensating events), 13 (3%) variceal bleeding, and 16 (4%) HE. The mean time to decompensation was 27 ± 20 months. No patient developed acute-on-chronic liver failure. Only 1 patient developed acute kidney injury, diagnosed simultaneously with ascites decompensation.

During follow-up, 31 patients developed PVT and 46 developed HCC before decompensation. Their follow-up was stopped at PVT/HCC diagnosis, censored as compensated and analyzed as competitive risk events.

No transjugular intrahepatic portosystemic shunt was placed (neither for PVT, as follow-up was stopped at PVT diagnosis), and no patient died before decompensation or was transplanted (neither for HCC, as follow-up was stopped at HCC diagnosis).

Patients on NSBBs had a significantly lower rate of decompensation than patients off NSBBs (16% vs 44%; HR, 0.28; 95% CI, 0.19–0.43; $P < .0001$) (Table 1, Figure 1*A*).

In patients with GEVs of any size (n = 299), decompensation occurred in 28 (17%) of 163 vs 61 (45%) of 136 of patients on-NSBBs vs off-NSBBs (HR, 0.30; 95% CI, 0.19–0.48; $P < .0001$) (Supplementary Figure 2*A*). In patients with small GEVs (n = 206), decompensation occurred in 17 (17%) of 99 vs 46 (43%) of 107 for the on-NSBBs and off-NSBBs groups (HR, 0.31; 95% CI, 0.18–0.55; $P < .0001$) (Figure 1*B*). In patients with medium-large GEVs (n = 93), decompensation occurred in 11 (17%) of 64 vs 15 (52%) of 29 for patients on-NSBBs vs on-EVL (HR, 0.26; 95% CI, 0.12–0.58; $P < .0001$) (Supplementary Figure 2*B*).

In patients with SPSS only (n = 107), decompensation occurred in 2 (8%) of 24 vs 36 (43%) of 83 for the on-NSBBs and off-NSBBs groups (HR, 0.15; 95% CI, 0.37–0.64; $P = .002$) (Figure 1*C*).

The benefit was maintained even when NSBBs users were considered as nonusers for the first follow-up year (Supplementary Materials).

Decompensation According to Etiology of Cirrhosis

Patients with viral-treated etiology experienced lower rate of decompensation than patients with alcohol- or MASLD-related etiology (HCV sustained virological response accounted for the 21% of the decompensation

Table1. Patients Characteristics at Inclusion and Outcomes of Interest

	On-NSBBs (n = 187)	Off-NSBBs (n = 219)	*P*
Baseline characteristics			
Male	122 (65.2)	140 (63.9)	.783
Age, y	62.24 ± 11.26	61.57 ± 11.29	.770
Etiology			.223
Alcohol related	20 (10.7)	37 (16.9)	
HCV-SVR	86 (46.0)	93 (42.4)	
HBV on NUC	32 (17.1)	28 (12.8)	
MASLD	28 (15.0)	26 (11.9)	
Miscellanea	21 (11.2)	35 (16.0)	
Arterial hypertension	84 (44.9)	93 (42.5)	.677
Diabetes	69 (36.7)	69 (31.5)	.253
White blood cell count ($\times 10^3$/mmc)	4842.80 ± 1871.26	5191.20 ± 1947.83	.068
Hemoglobin, g/dL	13.03 ± 1.93	12.85 ± 1.85	.348
Platelet count ($\times 10^3$/mmc)	102.32 ± 51.51	118.96 ± 56.15	.002[a]
AST, IU/L	37.31 ± 16.43	39.57 ± 16.83	.173
ALT, IU/L	29.66 ± 15.44	31.43 ± 15.88	.258
Bilirubin, mg/dL	1.31 ± 0.56	1.25 ± 0.55	.300
Albumin, g/L	3.82 ± 0.49	3.77 ± 0.50	.337
INR	1.20 ± 0.11	1.19 ± 0.14	.670
Creatinine, mg/dL	0.82 ± 0.21	0.80 ± 0.21	.299
Sodium, mmol/L	139.42 ± 2.80	138.93 ± 2.88	.083
Child-Pugh score	5.51 ± 0.73	5.57 ± 0.75	.410
Child-Pugh score, class			.667
Child-Pugh class A	160 (85.6)	184 (84.0)	
Child-Pugh class B (all B7)	27 (14.4)	35 (16.0)	
MELD*	9.77 ± 1.89	9.60 ± 1.95	.383
MELD-Na	10.81 ± 2.44	10.94 ± 2.61	.616
GEVs			<.0001[a]
No GEVs (SPSS only)	24 (12.8)	83 (37.9)	
Small GEVs	99 (52.9)	107 (48.9)	
Medium-large GEVs	64 (34.3)	29 (13.2)	
HCC	7 (3.7)	9 (4.1)	.850
PVT	7 (3.7)	5 (2.3)	.757
Treatments			
NSBBs			NA
Propranolol	144 (77.0)	NA	
Propranolol dose, mg/d	61.9 ± 9.1	NA	
Carvedilol	43 (23.0)	NA	
Carvedilol dose, mg/d	12.3 ± 4.2	NA	
Endoscopic variceal ligation	NA	29 (13.2)	NA
Statins	30 (16.0)	32 (14.6)	.690
Outcomes			
Decompensation-overall	30 (16.0)	97 (44.3)	<.0001[a]
Decompensation type			<.0001[a]
Ascites	22 (11.8)	76 (34.7)	
Bleeding	5 (2.7)	8 (3.7)	
HE[b]	3 (1.6)	13 (5.9)	
PVT (new or worsening)	17 (9.1)	14 (6.4)	.314
HCC (new diagnosis)	26 (13.9)	20 (9.1)	.131
Bacterial infections	25 (13.4)	59 (26.9)	.0001[a]

Values are n (%) or mean ± SD. Comparisons between groups were performed by means of Student's *t* test or the chi-square test when appropriate.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GEV, gastroesophageal varix; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; INR, international normalized ratio; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease–Sodium; NA, not applicable; NSBB, nonselective beta-blocker; NUC, nucleos(t)ide analogue; PVT, portal vein thrombosis; SPSS, spontaneous portosystemic shunt; SVR, sustained virological response.
[a]Statistically significant.
[b]All patients diagnosed with HE had signs compatible with West Haven criteria III or IV, no patient had signs of HE compatible with West Haven criteria II.

rate, HBV-on-nucleos[t]ide analogue 26%, alcohol 44%, MASLD 46%; $P < .0001$).

Despite different rates of decompensation, the benefit of NSBBs in reducing first decompensation was significant in each different etiology, including patients with HCV sustained virological response cirrhosis (n = 179) (HR, 0.24; 95% CI, 0.11–0.52; *P* by Gray test < .0001) (Figure 2*A*), HBV-related cirrhosis (n = 60) (HR, 0.38; 95%

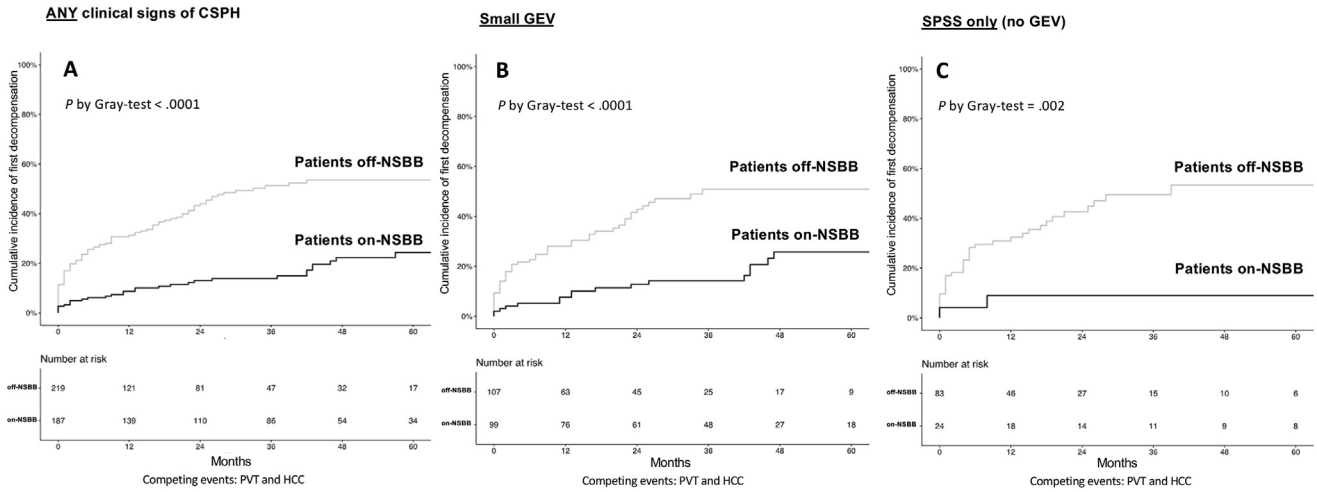

Figure 1. NSBBs benefit in patients with compensated cirrhosis and clinical signs of CSPH: (*A*) any signs of CSPH, (*B*) small GEVs, and (*C*) SPSSs only (no GEVs).

CI, 0.14–1.02; $P = .044$), alcohol-related cirrhosis (n = 57) (HR, 0.38; 95% CI, 0.14–1.03; $P = .043$) (Supplementary Figure 3*A* and *B*), and MASLD-related cirrhosis (n = 54) (HR, 0.30; 95% CI, 0.13–0.71; $P = .004$) (Figure 2*B*).

Decompensations in Patients With Cirrhosis Without HCC and/or PVT at Inclusion

The analysis performed by discarding patients with HCC and/or PVT at inclusion led to very similar results for patients with different signs of PH and for patients with different etiology of cirrhosis (Supplementary Figures 4 and 5).

Predictors of First Decompensation

Patients who decompensated had lower levels of hemoglobin and platelets count and higher Child-Pugh, Model for End-Stage Liver Disease (MELD), and MELD-Sodium score (Supplementary Table 2). The presence of diabetes was significantly higher in patients who decompensated (45% vs 30%; $P = .014$).

At univariate analysis (Table 2) viral-treated etiology and NSBB use were protective factors for first decompensation. Multivariable Cox regression analysis (Table 2) showed that diabetes, alanine aminotransferase, Child-Pugh, MELD-Sodium scores, and bacterial

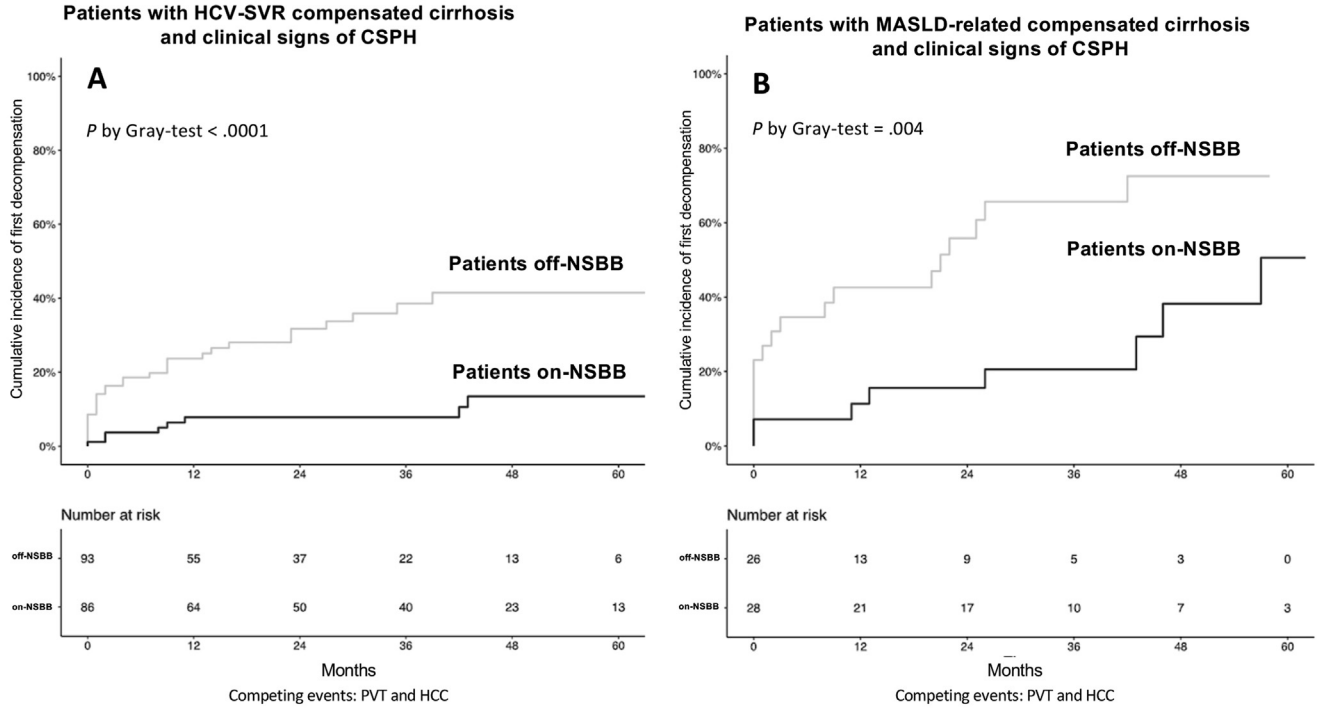

Figure 2. NSBBs benefit in patients with compensated cirrhosis of different etiologies. (*A*) HCV sustained virological response (SVR) compensated cirrhosis; (*B*) MASLD-related compensated cirrhosis.

Table 2. Cox Regression Analysis on Predictors of First Decompensation

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Etiology—viral	0.511 (0.360–0.726)	<.0001[a]	0.974 (0.660–1.438)	.895
Diabetes	1.619 (1.138–2.302)	.007[a]	1.587 (1.071–2.352)	.021[a]
Hemoglobin	0.771 (0.705–0.834)	<.0001[a]	0.850 (0.770–0.939)	.0001[a]
Platelet count	0.996 (0.993–1.000)	.037[a]	0.996 (0.992–1.000)	.031[a]
AST	1.027 (1.018–1.036)	<.0001[a]	0.997 (0.983–1.011)	.635
ALT	1.023 (1.013–1.033)	<.0001[a]	1.019 (1.004–1.034)	.014[a]
Child-Pugh score	1.964 (1.594–2.418)	<.0001[a]	1.774 (1.114–2.825)	.016[a]
Child-Pugh B (vs A)	2.735 (1.841– 4.062)	<.0001[a]	0.584 (0.270–1.263)	.172
MELD	1.261 (1.150– 1.383)	<.0001[a]	0.947 (0.806–1.112)	.506
MELD-Na	1.258 (1.174– 1.347)	<.0001[a]	1.121 (1.004–1.252)	.043[a]
NSBBs	0.282 (0.187–0.426)	<.0001[a]	0.320 (0.208–0.492)	<.0001[a]
Bacterial infections during follow-up	3.595 (2.520–5.128)	<.0001[a]	2.432 (1.652–3.581)	<.0001[a]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease–Sodium; NSBB, nonselective beta-blocker.
[a]Statistically significant.

infections were independent predictors of decompensation, while higher hemoglobin levels, higher platelets count, and NSBBs use were protective factors.

The receiver-operating characteristic curve analysis identified 12.5 g/dL as the best discriminating cutoff for hemoglobin in predicting decompensation.

Bacterial Infections

During follow-up, 84 (21%) patients had a total of 101 episodes of bacterial infections. Spontaneous bacteremia (24%), urinary tract infections (18%), and pneumonia (16%) were the most common (Supplementary Table 3). No bacterial infection led to NSBBs discontinuation.

Patients on NSBBs experienced a significant lower rate of bacterial infections (13% vs 27%; $P = .001$) (Table 1). At the multivariable Cox regression analysis (Table 3), only hemoglobin, Child-Pugh score, and NSBB use were independently associated with bacterial infections development.

Patients who decompensated had a significant higher rate of bacterial infections than those that remained compensated (44% vs 10%; $P < .0001$) (Supplementary Table 2). The competing risk factor

Table 3. Cox Regression Analysis on Predictors of Bacterial Infections During Follow-Up

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Etiology—viral	0.579 (0.3677–0.889)	.013[a]	0.955 (0.602–1.513)	.844
Diabetes	1.181 (0.748–1.863)	.475		
Gastroesophageal varices	0.647 (0.409–1.023)	.067		
Hemoglobin	0.839 (0.751–0.938)	.002[a]	0.868 (0.767–0.983)	.026[a]
Platelet count	1 (0.995–1.004)	.829		
Child-Pugh score	2.245 (1.741–2.896)	<.0001[a]	2.100 (1.490–2.960)	<.0001[a]
MELD	1.261 (1.127– 1.410)	<.0001[a]	1.022 (0.887–1.178)	.760
NSBBs	0.347 (0.217–0.556)	<.0001[a]	0.363 (0.225–0.586)	<.0001[a]

CI, confidence interval; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; NSBB, nonselective beta-blocker.
[a]Statistically significant.

analysis exploring the interrelationship between bacterial infections, NSBBs use, and first decompensation showed that patients off-NSBBs that had at least 1 episode of bacterial infection were significantly more prone to decompensate (73% of decompensation rate), while the lowest decompensation rate (10%) was experienced by patients on NSBBs with no episodes of bacterial infections (HR, 2.08; 95% CI, 1.73–2.49; $P < .0001$) (Figure 3).

Discussion

Our study shows that NSBBs are beneficial in reducing first decompensation onset in patients with cirrhosis and CSPH with treated etiology.

Recent findings have already shown that NSBBs can prevent first hepatic decompensation,[4] but the landmark study[6] was conducted before the availability of DAA treatment for HCV and only in patients with CSPH (detected by HVPG), with no or small varices. Moreover, the HVPG is not universally available. Similar accessibility challenges stand for noninvasive surrogate tools of PH like transient elastography. To address these challenges, we investigated the role of NSBBs in preventing first decompensation considering only patients with compensated cirrhosis and clinical features of CSPH (GEV and/or SPSS) after etiological treatment.

Main Finding

We collected data from our monocentric cohort of patients with compensated cirrhosis and detailed baseline characteristics and outcomes with a sample size larger than those from previous NSBBs trials. After a mean follow-up of almost 3 years, patients on-NSBBs experienced a significantly lower rate of first hepatic decompensation. Similarly to the Study on B-Blockers to Prevent Decompensation in Cirrhosis with Portal Hypertension (PREDESCI) trial,[6] the main decompensating event was ascites, with an incidence of 24% in our cohort, higher than the one reported in the PREDESCI trial, as our patients had signs of a probably more pronounced PH (higher rate of GEVs, presence of medium-large GEVs), but still significantly lower in patients on NSBBs. This confirms the benefit of NSBBs in reducing the onset of all decompensating events including ascites, in a cohort of patients with treated or metabolic etiology.[6] When stratified according to the type of PH clinical sign, the benefit of NSBBs was consistent across all subgroups, even in patients without GEVs but with SPSSs. We find these results particularly noteworthy, as they represent the first evidence of the potential benefit of NSBBs in patients without GEVs but with SPSSs. In the PREDESCI trial, the benefit of NSBBs was particularly pronounced in patients with GEVs with no clear description whether patients without GEVs had other signs of CSPH (other than HVPG $\geq$10 mm Hg), like the presence of SPSSs.

The benefit of NSBBs on first decompensation was significant across all different etiologies of cirrhosis. We confirmed that patients with viral-treated etiology have a significant lower rate of decompensation than those with alcohol- or MASLD-related etiologies. However, those patients in whom CSPH persisted after etiological treatment remained at risk of decompensation (although lower) with the benefit from NSBBs still significant. Our results might seem to contradict those reported by Tosetti et al[7] questioning the benefit of NSBBs in patients with viral-treated etiology, as these patients might experience negligible rates of decompensation. They included, however, all patients with CSPH starting antiviral therapy. Because effective antiviral treatment leads to a long-term reduction of PH,[8] we think that our results are actually in line with those previously reported,[7] as we included only patients with persistent CSPH after viral eradication.

In addition to the well-known predictors of decompensation, we found that NSBBs use was independently associated with lower risk of first decompensation, while bacterial infections, diabetes, and low hemoglobin levels were associated with higher risk. Bacterial infections were found to be the strongest trigger of first decompensation, confirming the results by Villanueva et al.[14] We further explored whether this impact could have been mitigated by NSBB use. NSBBs reduced the incidence of bacterial infections-related hospital admission in patients with decompensated cirrhosis[15] and of spontaneous bacterial peritonitis in patients with ascites,[16] but never associated with lower risk of bacterial infections in compensated cirrhosis.[14] Instead, in our cohort, probably due to a large sample size, patients on-NSBBs experienced lower rates of bacterial infections, and even those patients on-NSBBs experiencing bacterial infections showed lower rates of decompensation.

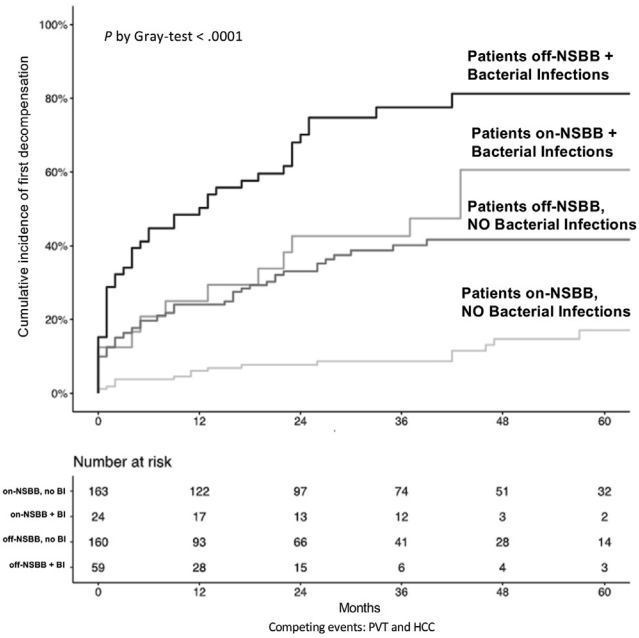

Figure 3. Impact of NSBBs and bacterial infections on the development of first decompensation.

Interestingly, diabetes emerged as a risk factor for decompensation independently from cirrhosis etiology. O'Beirne et al[17] recently demonstrated that diabetes leads to progression of liver disease up to decompensated cirrhosis in patients with nonalcoholic fatty liver disease. We further demonstrated the negative impact of diabetes on first decompensation regardless etiology. Patients with diabetes had worse outcomes independently from NSBBs use, and this confirms (in a larger cohort) recent findings[18] that diabetes impairs the hemodynamic response of NSBBs, triggering decompensation.

Surprisingly, hemoglobin was found as an independent predictor of first decompensation. Low hemoglobin levels have been previously reported as predictors of worse outcomes in patients with cirrhosis (in a cohort including both compensated and decompensated patients) with a cut-off of 10 g/dL[19] and as predictors of early hospital readmission in patients with acute decompensation with a cut-off of 8.7 g/dL.[20] We found a significant impact of low hemoglobin levels in patients with strictly compensated cirrhosis, in which a cut-off of 12.5 g/dL discriminated patients prone to decompensate. Given the independency from platelets count, the impact of low hemoglobin levels on decompensation might be explained not only by hypersplenism, but also probably by broader mechanisms, such as spleen destructions, PH-related gastropathy, and lower iron/vitamin absorption, leading to increased cardiac output and triggering decompensation. Due to the observational nature of our study, we can only speculate on the possible mechanisms through which hemoglobin levels impact outcome, but to our knowledge, these are the first data showing a negative impact of relatively low hemoglobin levels even in patients with strictly compensated cirrhosis.

Strengths/Limits of Our Study

We confirmed the benefit of NSBBs in a large monocentric cohort of patients with compensated cirrhosis. We reported predictors and triggers for first decompensation. By considering our selection criteria, based on clinical signs of CSPH, our results can be applied in centers in which HVPG or liver stiffness measurement are lacking. Limitations of our study are inherent to its observational nature. Some important data such as body mass index were not uniformly collected, and the impact of obesity on first decompensation could not be explored. Nutritional status assessment was also not available for all patients to properly understand the nature of hemoglobin levels. Although the percentage of patients with alcohol-related etiology was low, data on alcohol consumption for some patients could not be adequately explored. Finally, being a study grounded in clinical practice, patients on-NSBBs were not compared with a placebo group. Only in patients with medium-large GEVs, the NSBBs group was compared with patients on-EVL, which, however, could only lower the incidence of first variceal bleeding.

Conclusions

Our findings hold substantial clinical relevance. We confirmed the benefit of NSBBs in preventing all types of decompensating events in a large cohort of patients with compensated cirrhosis and clinical signs of enduring CSPH following etiological treatment.

We explored the interaction between NSBBs and triggers of first decompensation like bacterial infections, finding an interconnection and a benefit for patients on NSBBs that may go beyond their pure hemodynamic effects on PH.

Furthermore, we found new predictors of first decompensation that could pave the way to prospective studies investigating the impact of the whole nutritional status on first decompensation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2024.08.012.

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Laura Turco: study concept and design; acquisition of data; analysis and interpretation of data; technical and material support; statistical analysis; study supervision; drafting the manuscript, critical revision of the manuscript for important intellectual content and preparation of the final version of the manuscript. Madalina-Gabriela Taru: study design; acquisition and interpretation of data; technical and material support; study supervision; critical revision of the manuscript. Giovanni Vitale, Federica Mirici Cappa, Sonia Berardi, Anna Baldan, Roberto Di Donato, Paolo Pianta, Vittoria Vero, Luca Vizioli: acquisition of data. Horia Stefanescu, Lucia Maria Procopciuc, Bogdan Procopet: interpretation of data; critical revision of the manuscript for important intellectual content. Maria Cristina Morelli, Fabio Piscaglia: interpretation of data; technical and material support; study supervision; critical revision of the manuscript for important intellectual content and preparation of the final version of the manuscript. All authors reviewed and approved the final manuscript.

Conflicts of Interest
The authors disclose no conflicts.

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Supplementary Materials

Adherence to Therapies

Adherence to etiological therapies was checked at every single visit in the 2 years before enrollment and during follow-up as follows:

- Patients with viral etiology had their hepatitis C virus (HCV) RNA and/or hepatitis B virus DNA checked at every visit.
- Alcohol abstinence was assessed at every visit in all patients (not only in those with pure alcohol-related cirrhosis, although with deeper attention to this last group) and laboratory tests checked for consistency. The majority of them had also their alcohol abstinence confirmed by quantitative biomarkers like etylglucuronid or phosphatidylethanol.
- For patients with autoimmune disease, stable remission under specific treatment was checked at every visit as consistent laboratory tests.
- For patients with metabolic dysfunction–associated steatotic liver disease–related cirrhosis, as specified in the Patients and Methods, there is still no definitive etiological treatment apart from weight loss, which is very rarely achieved. For the interest of the current study, in order to have patients not to dissimilar from the other etiologies, we only included those that were under treatment for diabetes, hypercholesterolemia, and/or arterial hypertension (if clinically indicated) with stable control of these cofactors and body weight over time, confirmed by no worsening of laboratory tests and controlled blood pressure both in the 2 years before enrollment and during follow-up.

Adherence to nonselective beta-blockers (NSBBs) was checked at every single visit by enquiring with the patients and verifying blood pressure/heart rate for consistency.

No patient included in the study had signs/was suspect to not be adherent to therapies (both etiological and NSBBs).

Radiological Assessment of Spontaneous Portosystemic Shunts

Spontaneous portosystemic shunts (SPSSs) were detected by abdominal computed tomography scan during the portal venous phase, a postcontrast acquisition performed 70 seconds after the contrast agent injection, and defined as spontaneous communications between the spleno-mesenteric-portal axis and the systemic venous system, excluding gastroesophageal varices (GEVs). A minimum diameter of 5 mm was required in order to make an accurate diagnosis of SPSS. Each SPSS was evaluated in multiple planes (axial, coronal, sagittal). In patients with more than 1 shunt, the shunt with the largest diameter (measured with automatic vessel segmentation techniques) was considered the dominant shunt and classified according to the site of connection as paraumbilical, splenorenal, gastrorenal, mesorenal, or mesocaval shunt.

Definitions of Hepatic Decompensation

Variceal bleeding was defined as an episode of hematemesis/melena with confirmed active bleeding from a varix observed at endoscopy or when a sign of recent bleeding, such as a "white nipple," is observed at endoscopy.[e1]

Ascites was defined according to the International Club of Ascites by compatible signs on physical examination, confirmed by cross-sectional imaging. The presence of ascites detected only on ultrasonography was not considered a decompensating event.

Overt hepatic encephalopathy was defined as signs compatible with West Haven criteria $\geq$II.

Definitions of Bacterial Infections

Patients in whom bacterial infections was suspected based in the presence of clinical symptoms (ie, fever, dysuria, urinary urgency and/or frequency, diarrhea, or new onset of cough) underwent screening workup including physical examination; standard laboratory test looking for neutrophilic leukocytosis, increase of C-reactive protein, increase of procalcitonin; fresh urine sediment and urine cultures; chest x-ray film; bacterial cultures of blood; stool cultures in case of diarrhea; and skin samples in case of suspected cellulitis.

The diagnoses of urinary tract infection, bacterial-related diarrhea, and respiratory infections were made according to the presence of clinical symptoms and simultaneous related positive cultures (urine or stool) or chest x-ray film.

The diagnosis of cellulitis was based on clinical symptoms and positive skin samples.

Bacteremia was considered spontaneous when positive blood cultures were obtained in the absence of a known source of infection.

Bacteria isolated in positive cultures were tested for antibiotic susceptibility.

NSBBs Users Considered as Nonusers for the First Year of Follow-Up

Patients on NSBBs had a significantly lower decompensation rate than patients off NSBBs (hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.21–0.62; $P < .0001$), and this benefit was maintained in patients with different clinical signs of clinically significant portal hypertension:

- In patients with GEVs of any size (n = 299), decompensation was lower in the on-NSBBs group compared with the off-NSBBs group (HR, 0.37; 95% CI, 0.20–0.66; $P = .001$).
- Patients with small GEVs (n = 206) decompensation was lower in the on-NSBBs group compared with the off-NSBBs group (HR, 0.40; 95% CI, 0.20–0.82; $P = .01$).

- In patients with medium-large GEVs (n = 93) decompensation was lower in the on-NSBBs group compared with the on endoscopic variceal ligation group (HR, 0.29; 95% CI, 0.19-0.90; $P = .03$).
- In patients with SPSSs only (n = 107), decompensation was lower in the on-NSBBs group compared with the off-NSBBs group (HR, 0.18; 95% CI, 0.24-0.64; $P = .04$).

Relationship Between Liver Stiffness Measurement, NSBBs Use, and Rate of Decompensation

Among 406 patients included, 91 (22.4% of the population) had their liver stiffness measurement performed in the 12 months before the enrollment in the study.

Fifty-three patients had liver stiffness measurement $\geq$25 kPa (17 with medium-large GEVs, 25 with small GEVs, 11 presenting with SPSSs only), 28 (53%) of them were started on NSBBs.

During follow-up, 15 (28%) patients decompensated: 4 (14%) of 28 in the on-NSBBs group and 11 (44%) of 25 in the off-NSBBs group ($P = .01$).

Supplementary Reference

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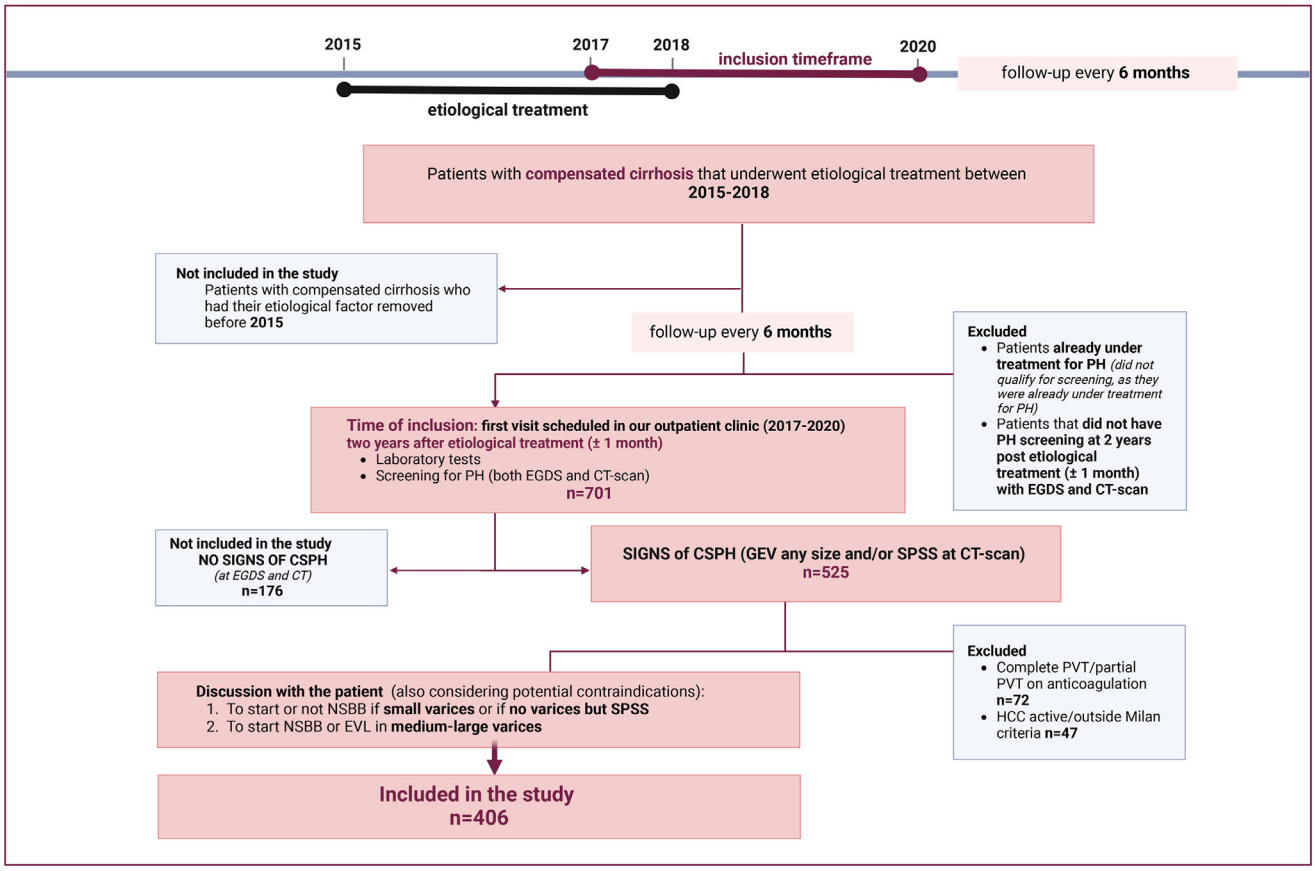
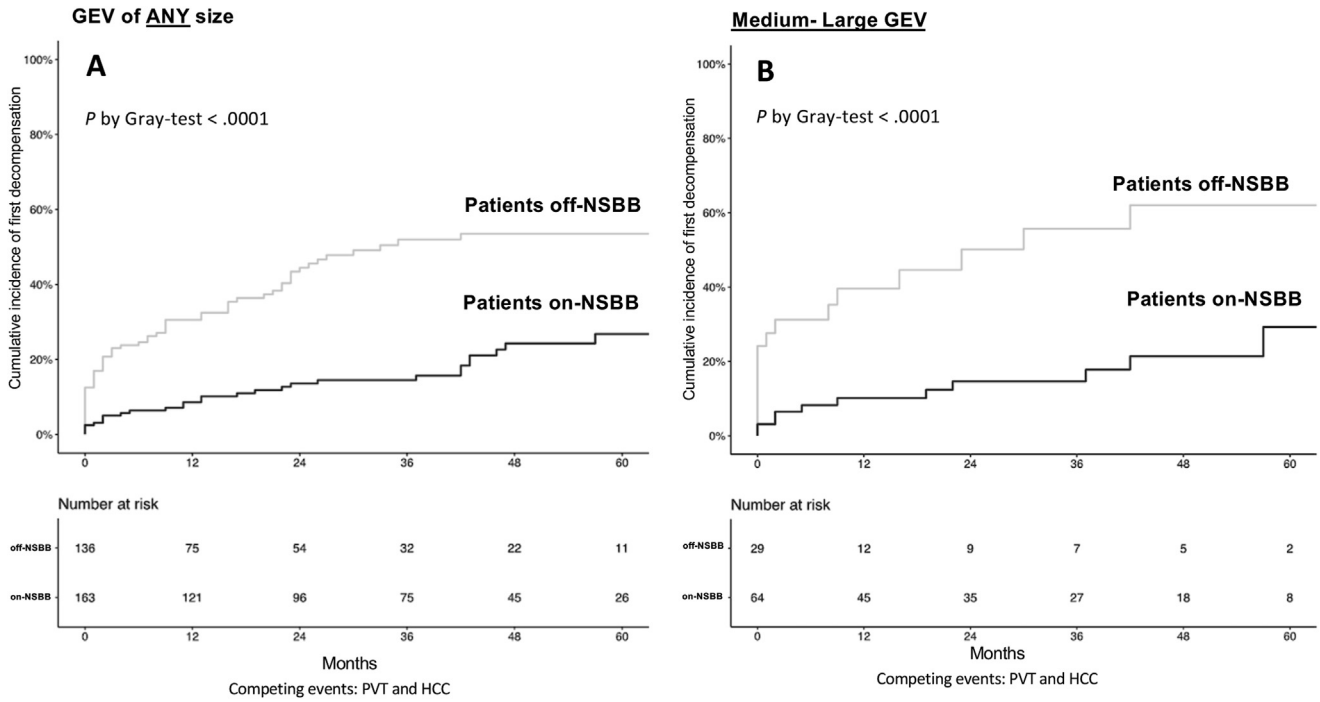
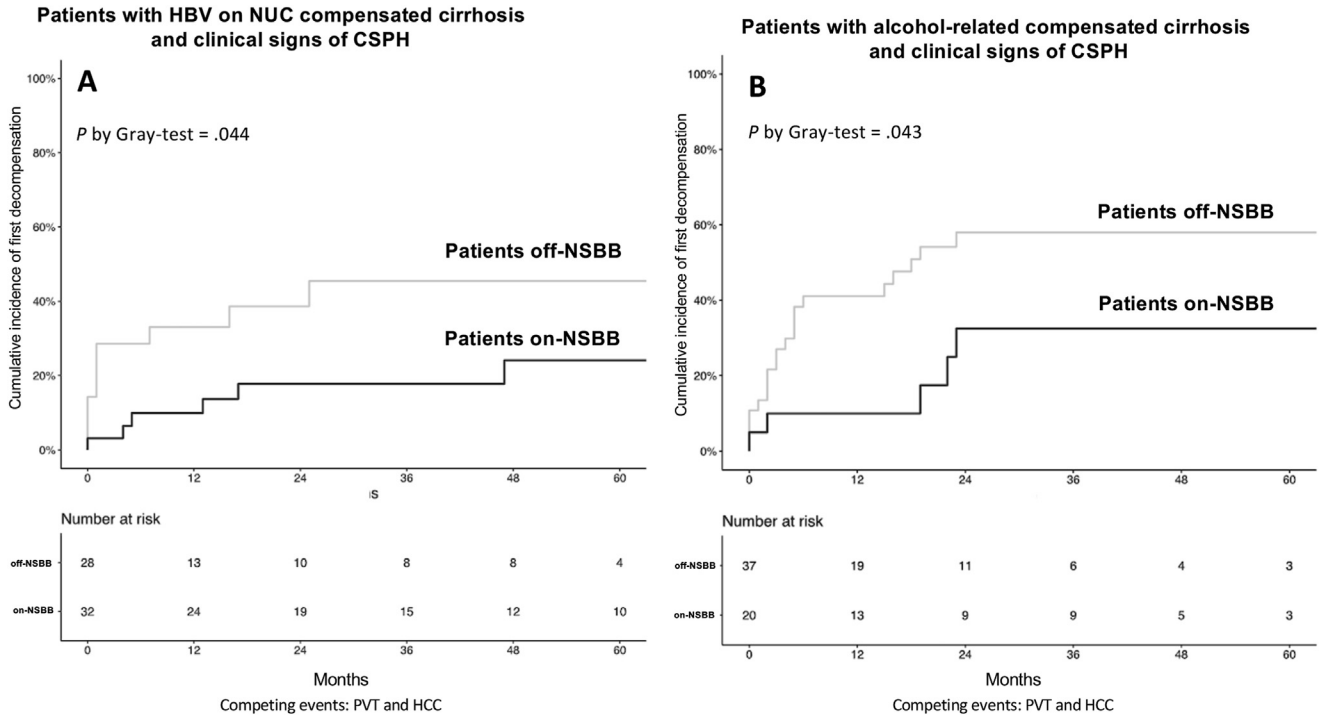


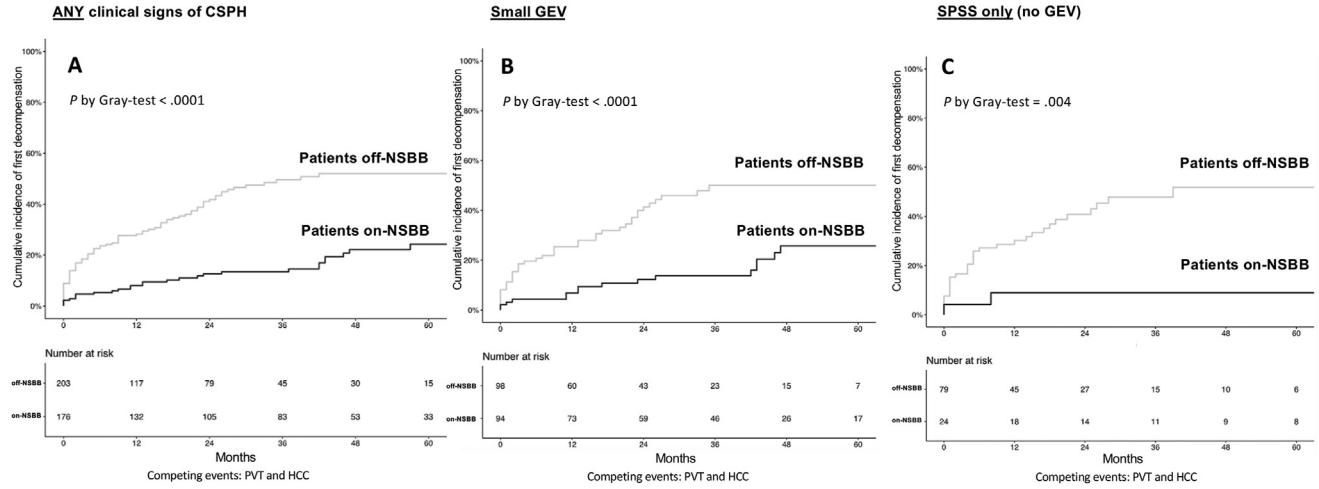
Supplementary Figure 1. Study methodology and flow chart. CT, computed tomography; EGDS, esofagogastroduodenoscopy; EVL, endoscopic variceal ligation; GEV, gastroesophageal varix; HCC, hepatocellular carcinoma; NSBB, nonselective beta-blocker; PH, portal hypertension; PVT, portal vein thrombosis; SPSS, spontaneous portosystemic shunt.



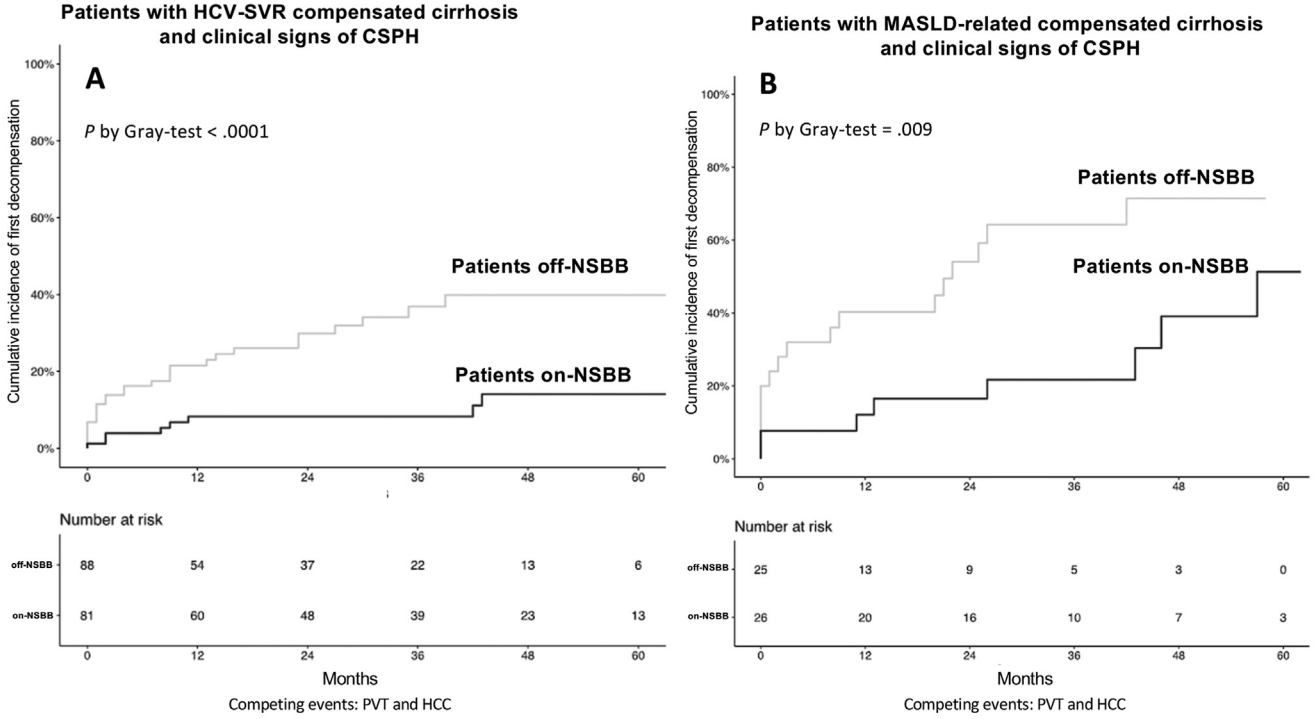
Supplementary Figure 2. Nonselective beta-blockers (NSBBs) benefit in patients with compensated cirrhosis and clinical signs of clinically significant portal hypertension (CSPH): (*A*) gastroesophageal varices (GEVs) of any size and (*B*) medium-large GEVs. HCC, hepatocellular carcinoma; PVT, portal vein thrombosis.



Supplementary Figure 3. Nonselective beta-blockers (NSBBs) benefit in patients with compensated cirrhosis of different etiologies: (*A*) hepatitis B virus on nucleos(t)ide analogue (HBV-on-NUC) compensated cirrhosis and (*B*) alcohol-related compensated cirrhosis. CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; PVT, portal vein thrombosis.



Supplementary Figure 4. Nonselective beta-blockers (NSBBs) benefit in patients with compensated cirrhosis and clinical signs of clinically significant portal hypertension (CSPH) without hepatocellular carcinoma (HCC) and/or portal vein thrombosis (PVT) at inclusion: (*A*) any signs of CSPH, (*B*) small gastroesophageal varices (GEVs), and (*C*) spontaneous portosystemic shunt (SPSS) only (no GEVs).



Supplementary Figure 5. Nonselective beta-blockers (NSBBs) benefit in patients with compensated cirrhosis of different etiologies without hepatocellular carcinoma (HCC) and/or portal vein thrombosis (PVT) at inclusion: (*A*) hepatitis C virus sustained virological resistance (HCV-SVR) compensated cirrhosis and (*B*) metabolic dysfunction–associated steatotic liver disease (MASLD)–related compensated cirrhosis. CSPH, clinically significant portal hypertension.

Supplementary Table 1. SPSS Classification

	Patients With SPSS ± GEVs (n = 281)	Patients With SPSS With GEVs (n = 174)	Patients With SPSS With No GEVs (n = 107)
Paraumbilical vein recanalization	163 (58%)	89 (51%)	74 (69%)
Splenorenal shunt	78 (28%)	53 (30%)	25 (23%)
Gastrorenal shunt	11 (4%)	8 (5%)	3 (3%)
Mesorenal shunt	14 (5%)	12 (7%)	2 (2%)
Mesocaval shunt	15 (5%)	12 (7%)	3 (3%)

Values are n (%).
GEV, gastroesophageal varix; SPSS, spontaneous portosystemic shunt.

Supplementary Table 2. Patients Characteristics at Inclusion and Bacterial Infection Rates Before Decompensation, Stratified According to Decompensation Status During Follow-Up

	No Decompensation During Follow-Up (n = 279)	Decompensation During Follow-Up (n = 127)	*P*
Male	184 (65.9)	78 (71.4%)	.376
Age, y	61.15 ± 11.41	62.02 ± 10.97	.476
Etiology			<.0001[a]
Alcohol	32 (11.5)	25 (19.7)	
HCV-SVR	141 (50.5)	38 (29.9)	
HBV on NUC	43 (15.4)	17 (13.4)	
MASLD	29 (10.4)	25 (19.7)	
Miscellanea	34 (12.2)	22 (17.3)	
Arterial hypertension	115 (41.2)	62 (48.8)	.141
Diabetes	84 (30.1)	54 (45.2)	.014[a]
White blood cell count ($\times 10^3$/mmc)	5034.31 ± 1860.26	5022.80 ± 2048.21	.955
Hemoglobin, g/dL	13.24 ± 1.82	12.25 ± 1.88	<.0001[a]
Platelet count ($\times 10^3$/mmc)	115.34 ± 55.91	102.41 ± 50.82	<.0001[a]
AST, IU/L	35.39 ± 15.56	45.43 ± 16.99	<.0001[a]
ALT, IU/L	28.49 ± 15.31	35.28 ± 15.54	<.0001[a]
Bilirubin, mg/dL	1.21 ± 0.55	1.41 ± 0.53	.0001[a]
Albumin, g/L	3.92 ± 0.46	3.51 ± 0.46	<.0001[a]
INR	1.18 ± 0.13	1.23 ± 0.11	<.0001[a]
Creatinine, mg/dL	0.81 ± 0.20	0.82 ± 0.25	.843
Sodium, mmol/L	139.45 ± 2.72	138.52 ± 3.02	.002[a]
Child-Pugh score	5.41 ± 0.67	5.85 ± 0.81	<.0001[a]
Child-Pugh score			<.0001[a]
Child class A	251 (90.0)	93 (73.2)	
Child class B (all B7)	28 (10.0)	34 (26.8)	
MELD	9.38 ± 1.93	10.35 ± 1.75	<.0001[a]
MELD-Na	10.42 ± 2.46	11.91 ± 2.41	<.0001[a]
GEVs, any size	210 (75.3)	89 (70.1)	.271
GEVs			.492
No varices (SPSS only)	69 (24.7)	38 (29.9)	
Small varices	143 (51.3)	63 (49.6)	
Medium-large varices	67 (24.0)	26 (20.5)	
HCC at baseline	8 (2.9)	8 (6.3)	.099
PVT at baseline	7 (2.5)	5 (3.9)	.431
NSBB	157 (56.2)	30 (23.6)	<.0001[a]
Statins	47 (16.8)	15 (11.8)	.191
Patients experiencing bacterial infections during follow-up, before decompensation	28 (10.0)	56 (44.1)	<.0001[a]

Values are n (%) or mean ± SD. Comparisons between groups were performed by means of Student's *t* test or the chi-square test when appropriate.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GEV, gastroesophageal varix; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease–Sodium; NSBB, nonselective beta-blocker; NUC, nucleos(t)ide analogue; PVT, portal vein thrombosis; SPSS, spontaneous portosystemic shunts; SVR, sustained virological response.
[a]Statistically significant.

Supplementary Table 3. Bacterial Infections in Patients On vs Off NSBBs

	On NSBBs (n = 187)	Off NSBBs (n = 219)
Number of patients that developed at least 1 episode of bacterial infection	25 (13.4)	59 (26.9)
Number of patients that developed 2 or more episodes of bacterial infection	4 (2.1)[a]	10 (4.6)[b]
Number of total episodes of bacterial infections (n = 101)	29	72
Type of bacterial infections		
Spontaneous bacteremia (n = 24)	7	17
Urinary tract infection (n = 18)	5	13
Pneumonia (n = 16)	3	13
Bacterial related diarrhea (n = 15)	5	10
Cellulitis (n = 13)	4	9
Other (n = 15)	5	10

Values are n (%) or n.
NSBB, nonselective beta-blocker.
[a]All of them developed 2 episodes of bacterial infections before decompensation.
[b]7 patients developed 2 episodes of bacterial infections before decompensation, 3 patients developed 3 episodes of bacterial infections before decompensation.