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## Retrospective Cohort Study

**Beta-blockers and physical frailty in patients with end-stage liver disease**

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**Abstract****AIM**

To investigate beta-blocker (BB) use in patients with cirrhosis and determine their effects on physical frailty and overall survival.

**METHODS**

Adult outpatients with cirrhosis listed for liver transplantation underwent testing of physical frailty using the performance-based Liver Frailty Index, comprised of chair stands, grip strength, and balance testing, as well as self-reported assessments of exhaustion and physical activity. BB use was assessed from medical chart review. Univariable and multivariable logistic regression were performed to determine BB use and their association with measures of physical frailty. Competing risk analyses were performed to determine the effect of BB use on wait-list mortality, as defined by death or delisting for being too sick for transplant.

**RESULTS**

Of 344 patients, 35% were female, median age was 60, median model for end stage liver disease was 15, and 53% were prescribed a BB. Compared to those not on

BB, patients on BB were similar except for percentage female (25% *vs* 46%;  $P < 0.001$ ) and BMI (29 *vs* 28;  $P = 0.008$ ). With respect to tests of physical frailty, BB use was not associated with increased odds of frailty (by the Liver Frailty Index), exhaustion, or low physical activity. BB use was, however, significantly associated with a decreased adjusted risk of mortality (SHR 0.55;  $P = 0.005$ ).

### CONCLUSION

In patients with cirrhosis awaiting liver transplantation, BB use is not associated with physical frailty. We confirmed the known survival benefits with BB use, and concerns about adverse effects should not deter their utilization when indicated.

**Key words:** Beta-blockers; Cirrhosis; End-stage liver disease; Frailty

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**Core tip:** In patients with cirrhosis, beta-blockers are the main medical treatment for prevention of variceal bleeds, but fatigue and weakness are commonly reported side effects. This study demonstrates that use of beta-blockers is not associated with physical frailty and improves survival in patients with cirrhosis.

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## INTRODUCTION

Physical frailty is reported to be prevalent in patients with cirrhosis and has emerged as a critical determinant of outcomes in this population<sup>[1-3]</sup>. Resulting from the loss of homeostatic balance of multiple physiologic systems including (but not limited to) musculoskeletal, inflammatory, endocrine, and neurocognitive, physical frailty has been operationalized using standardized instruments that measure multiple domains such as fatigue, weakness, slowness, weight loss, and low activity<sup>[4]</sup>. Two of these physical frailty components, fatigue and weakness, overlap with the frequent side effects of non-selective beta-blockers (BBs).

This overlap is of particular importance for patients with cirrhosis. Beta-blockers are the main pharmacologic therapy for both primary and secondary prevention of variceal hemorrhage in patients with cirrhosis<sup>[5]</sup>. Despite the proven clinical effectiveness and known mortality benefits of beta-blockers, there is mounting evidence that patients are not receiving these treatments due to physicians under prescribing, suboptimal adherence,

and side effects. More recently, investigators have hypothesized that a “therapeutic window” exists during which a patient with cirrhosis might benefit from beta-blocker therapy for variceal prevention, with a patient losing benefit once they develop refractory ascites<sup>[6,7]</sup>. One study showed that as few as 6%-22% of patients with known medium or large varices received primary prophylaxis with beta-blockers<sup>[8]</sup>. Furthermore, concern regarding side effects led to discontinuation of beta-blockers in about 15% of patients with cirrhosis<sup>[9]</sup>.

Reluctance to prescribe beta-blocker therapy may arise from concerns about their commonly reported symptoms of weakness and fatigue<sup>[10,11]</sup>. Most of the studies of beta-blocker side effects are performed within the cardiac population, but little is known of their effects in patients with cirrhosis. The adverse effects of weakness and fatigue, factors that are integral to the frail phenotype<sup>[4]</sup>, are of particular importance in this population given the recent studies indicating physical frailty as a predictor of mortality in patients awaiting liver transplant<sup>[2,3]</sup>. Therefore, in this study, we aimed to evaluate the association between beta-blocker use and physical frailty in patients with cirrhosis.

## MATERIALS AND METHODS

### Study population

The Functional Assessment in Liver Transplantation (FrAILT) study is an ongoing prospective study of adult patients ( $\geq 18$  years) with cirrhosis actively listed for liver transplantation and seen as outpatients at the University of California, San Francisco (UCSF). This retrospective study included data from patients enrolled in the FrAILT study from July 2012 until January 2014. Included were patients with model for end stage liver disease (MELD) score  $\geq 12$  and excluded were patients with severe hepatic encephalopathy, defined by the time to complete the Numbers Connection Test of  $> 120$  s. All participants gave informed consent and the UCSF Institutional Review Board approved this study.

### Study procedures and data collection

At enrollment and subsequent clinic visits, all patients underwent tests of physical frailty in the outpatient clinic setting: (1) the Liver Frailty Index (LFI), consisting of chair stands, grip strength, and balance (calculator available at <https://liverfrailtyindex.ucsf.edu>)<sup>[11]</sup>; (2) exhaustion, determined by self-report using two questions from the Center for Epidemiological Studies-Depression scale that have been included in the Fried Frailty Phenotype<sup>[4]</sup>; and (3) physical activity, determined by self-report using the Minnesota Leisure Time Physical Activity Scale (MNLTPA) that has also been included in the Fried Frailty Phenotype<sup>[4]</sup>.

Patient demographics, medical co-morbidities, degree of ascites, vital signs, beta-blocker use and beta-blocker indications were collected from the clinic visit note from the same date of their physical frailty

assessment. Hepatic encephalopathy (HE) was defined as moderate if the patient's Numbers Connection Test score was  $> 60$  s and mild/none if  $< 60$  s. Laboratory studies within 3 mo of the study visit were collected from the patient's electronic health record.

### Statistical analysis

Patients were classified as "frail" if they had an LFI score of  $\geq 4.5$ , as these cutoffs have been associated with worse outcomes in patients awaiting liver transplant<sup>[1]</sup>. Patients were classified as "robust" if they had an LFI score of  $< 3.2$ <sup>[1]</sup>. Frailty by the MNLTPA activity level was defined as  $< 383$  Kcal/wk for males and  $< 270$  Kcal/wk for females<sup>[4]</sup>.

Differences in baseline characteristics between beta-blocker users vs non-users were compared using chi-square or Wilcoxon ranksum tests for categorical and continuous variables, respectively. Differences in heart rate, performance measures of physical frailty, and self-reported physical frailty were also compared by chi-square and Wilcoxon ranksum tests. Univariable logistic regression was performed to determine associations between beta-blocker use and physical frailty. Multivariable models initially included heart rate, age, MELD, creatinine, albumin, sodium, presence of hepatocellular carcinoma (HCC), degree of ascites, and presence of hepatic encephalopathy. All variables associated with a  $P$ -value  $< 0.2$  in the univariable analysis were included in the multivariable model and a backwards stepwise selection was used to only include variables with a  $P < 0.05$ .

Competing risk analysis evaluated the effect of beta-blocker use on wait-list mortality, as defined by death or delisting for being too sick for transplant, with liver transplant as a competing risk. Patients were censored at the time of waitlist removal if removed for "other" reasons (*e.g.*, violation of substance abuse contract, inadequate social support). All variables associated with a  $P$ -value  $< 0.2$  in the univariate analysis were included in the multivariate model and a backward stepwise selection was used to eliminate covariates using a threshold  $P$ -value  $< 0.05$  to determine the subdistribution hazard ratio (SHR).

All statistical analyses were performed using STATA<sup>®</sup> version 11 (College Station, TX, United States). The statistical methods of this study were reviewed by Lai JC, MD, from UCSF who is trained in advanced clinical research methodologies.

## RESULTS

### Baseline characteristics of the cohort

A total of 344 patients with end-stage liver disease were included in this study. Baseline characteristics are listed in Table 1, column A. The median (IQR) age was 60 years (54-64) and 35% were female. The etiology of underlying liver disease was hepatitis C in 50%, alcoholic liver disease in 15%, nonalcoholic steatohepatitis in 13%,

autoimmune/cholestatic liver disease in 11%, hepatitis B in 4% and "other" in 6%. Median weight and body mass index (BMI) were 83.5 kg and 28.4 kg/m<sup>2</sup>, respectively. With respect to medical co-morbidities, 44% had hypertension, 32% had diabetes, and 7% had coronary artery disease. Hepatic encephalopathy was present in 21% of patients. Ascites was absent in 67%, 30% had a mild to moderate degree, and 3% had severe ascites. The median (IQR) MELD score was 15 (12-18), and the proportion with Child Pugh Score A, B, and C was 19%, 60%, and 21%, respectively.

### Characteristics associated with beta-blocker use

Out of the 344 patients, 181 (53%) were taking a beta-blocker at the time of assessment: 68% were taking propranolol, 15% nadolol, and 17% other beta-blockers (Supplemental Table 1).

Baseline characteristics of beta-blocker users vs non-users are shown in Table 1, columns B and C, respectively. The two groups were similar with respect to age, race/ethnicity, etiology of liver disease, degree of ascites, rates of hepatic encephalopathy, MELD scores and Child Pugh scores. Beta-blocker users vs non-users had a lower percentage of females (25% vs 46%;  $P < 0.001$ ), higher body mass index (29.3 kg/m<sup>2</sup> vs 27.7 kg/m<sup>2</sup>;  $P = 0.008$ ), and higher rates of HCC (32% vs 22%;  $P = 0.04$ ).

Median (IQR) heart rate (in beats per minute) differed significantly between beta-blocker users and non-users [67 (61-74) vs 76 (69-85);  $P < 0.001$ ]. There was no significant difference in systolic or diastolic blood pressure between the two groups.

### Associations between beta-blocker use and physical frailty

A comparison of characteristics by beta-blocker use is presented in Table 2. Median LFI was statistically, but not clinically, significantly worse in beta-blocker users compared to non-users (3.75 vs 3.64;  $P = 0.04$ ). Rates of frailty were similar between the two groups (14% vs 14%), but there was a trend toward a lower rate of patients who were classified as robust among beta-blocker users vs non-users (16% vs 25%;  $P = 0.06$ ). There was no difference in rates of self-reported exhaustion or physical activity between the two groups (Table 2).

In univariable logistic regression, beta-blocker use was not significantly associated with physical frailty as defined by LFI  $\geq 4.5$  [OR 0.99 (95%CI: 0.54-1.83)], exhaustion [OR 0.97 (95%CI: 0.63-1.48)], or low physical activity [OR 0.92 (95%CI: 0.60-1.41)]. The associations between beta-blocker use and physical frailty by LFI  $\geq 4.5$  [OR 0.97 (95%CI: 0.50-1.87)], exhaustion [OR 0.97 (95%CI: 0.63-1.50)], or low physical activity [OR 1.18 (95%CI: 0.74-1.89)] did not change after multivariable adjustment. There was no association between physical frailty and each unit increase in dosing of either propranolol [OR 1.00 (95%CI: 0.98-1.02)] or nadolol [OR 0.99 (95%CI: 0.92-1.08)].

**Table 1 Patient demographics**

Characteristics	All <i>n</i> = 344	On beta blockers <i>n</i> = 181 (53%)	Not on beta blockers <i>n</i> = 163 (47%)	<i>P</i> value
Age (yr)	60 (54-64)	61 (54-65)	60 (54-63)	0.16
Female	35%	25%	46%	< 0.001
Race/ethnicity				0.26
Non-Hispanic White	57%	56%	58%	
Black	4%	3%	6%	
Hispanic White	27%	30%	23%	
Asian	7%	5%	8%	
Other	6%	7%	5%	
Etiology of liver disease				0.39
Hepatitis C	50%	51%	49%	
Alcohol	15%	15%	15%	
Nonalcoholic steatohepatitis	13%	15%	11%	
Autoimmune/cholestatic	11%	9%	14%	
Hepatitis B	4%	2%	6%	
Other	6%	7%	6%	
HCC	27%	32%	22%	0.04
BMI (kg/m <sup>2</sup> )	28.4 (24.9-33.0)	29.3 (25.8-33.7)	27.7 (24.2-31.8)	0.0081
Medical co-morbidities				
Hypertension	44%	48%	40%	0.12
Diabetes	32%	36%	27%	0.06
Coronary artery disease	7%	10%	4%	0.04
Lab tests				
Lab MELD	15 (12-18)	15 (13-18)	15 (12-18)	0.55
Total bilirubin (mg/dL)	2.3 (1.6-3.4)	2.3 (1.5-3.2)	2.4 (1.7-3.6)	0.41
INR	1.4 (1.2-1.6)	1.4 (1.3-1.6)	1.4 (1.2-1.6)	0.54
Creatinine (mg/dL)	0.9 (0.8-1.2)	1 (0.8-1.2)	0.9 (0.7-1.2)	0.0034
Sodium (mEq/L)	137 (134-139)	137 (135-139)	137 (134-139)	0.75
Ascites				
Mild-moderate	30%	30%	30%	0.40
Refractory	3%	4%	2%	
Hepatic encephalopathy <sup>1</sup>	21%	22%	21%	0.86
Child Pugh Score				0.89
A	19%	18%	20%	
B	60%	60%	59%	
C	21%	22%	21%	

<sup>1</sup>Defined as a Numbers Connection test > 60 s. HCC: Hepatocellular carcinoma; BMI: Body mass index; MELD: Model for End Stage Liver Disease.

**Table 2 Comparison of metrics of physical frailty by beta-blocker use**

Outcome	On beta blockers <i>n</i> = 181 (53%)	Not on beta blockers <i>n</i> = 163 (47%)	<i>P</i> value
Liver frailty index <sup>1</sup>	3.75 (3.37-4.15)	3.64 (3.23-4.04)	0.04
Chair stands (s)	12.5 (10-16.2)	10.9 (8.3-13.2)	0.003
Grip strength (kg)	33.3 (24.3-40)	29 (22-37)	0.03
Balance (s)	30 (30-30)	30 (26.6-30)	0.20
LFI Frail	14%	14%	0.98
LFI Robust	16%	25%	0.06
Exhaustion	51%	52%	0.89
MNLTPA frailty	58%	60%	0.69

<sup>1</sup>Five missing data points. LFI: Liver frailty index; MNLTPA: Minnesota leisure time physical activity scale.

### Beta-blocker use and wait-list mortality

Median (IQR) follow-up time was 12 (4-22) mo. By the end of follow-up, 92 (27%) patients died or were delisted for being too sick, 167 (48%) underwent liver transplant, 47 (14%) were delisted for other reasons, and 37 (11%) remained on the waitlist. Patients who were not beta-blocker users vs beta-blocker users had a higher proportion who died/delisted for being too sick

(33% vs 22%; *P* = 0.02).

In univariable competing risks regression, beta-blocker use was significantly associated with decreased mortality, whereas creatinine, HE and LFI score were significantly associated with increased waitlist mortality (Table 3). After adjustment for all independent predictors, beta-blocker use remained associated with decreased hazard of waitlist mortality [SHR 0.55 (95%CI 0.36-0.83)



**Table 3** Competing risks survival analysis

Variable	Univariable SHR (95%CI) P value	Multivariable SHR (95%CI) P value
Being on a Beta Blocker	0.57 (0.38-0.85) 0.006	0.55 (0.36-0.83) 0.005
Liver Frailty Index	1.52 (1.13-2.03) 0.005	1.35 (1.02-1.80) 0.04
MELD score	1.03 (0.99-1.07) 0.19	
Creatinine	1.17 (1.07-1.28) 0.001	1.10 (1.00-1.22) 0.006
Albumin	0.79 (0.56-1.12) 0.18	
Sodium	0.99 (0.95-1.04) 0.76	
HCC	0.80 (0.50-1.29) 0.37	
Ascites	0.98 (0.63-1.51) 0.92	
Age	1.02 (0.99-1.04) 0.15	
Gender (female)	1.09 (0.72-1.65) 0.68	
Hepatic encephalopathy (> 60 s)	1.99 (1.30-3.05) 0.001	1.64 (1.05-2.57) 0.03

HCC: Hepatocellular carcinoma; MELD: Model for End Stage Liver Disease; SHR: subdistribution hazard ratio.

$P = 0.005$ ].

## DISCUSSION

Non-selective beta-blockers have become a cornerstone of medical management for patients with cirrhosis to reduce the risk of variceal hemorrhage and have been associated with mortality benefit<sup>[9,12,13]</sup>. However, beta-blockers also have a number of well-known side effects, including fatigue and weakness, which may be particularly challenging for patients with cirrhosis who already experience a high burden of fatigue and weakness from their cirrhosis, in addition to polypharmacy<sup>[14]</sup>. These common side effects of non-selective beta-blockers could, in turn, theoretically accelerate physical frailty, a potent determinant of mortality in this population<sup>[1-3]</sup>.

In this study, we demonstrated that the addition of a beta-blocker is not associated with clinically-significantly increased rates of physical frailty or its associated symptoms of exhaustion or low physical activity. While patients on non-selective beta-blockers had *statistically* worse LFI scores than patients not on non-selective beta-blockers, the difference in the median values for each group was 0.11, which does not meet the 0.2 threshold for the minimum clinically important difference in LFI<sup>[15]</sup>. This is supported by the fact that rates of physical frailty, using the LFI cut-off of  $\geq 4.5$ <sup>[1]</sup>, were similar between the two groups. Furthermore, our analyses confirmed the known overall mortality benefits of beta-blocker therapy<sup>[9,12,13]</sup>. The fact that the vast majority of our cohort did not have refractory ascites supports

the concept of a “therapeutic window” for benefit of beta-blockers on mortality in patients with cirrhosis<sup>[7]</sup>. Importantly, our data add to the existing body of literature by adjusting for the differences in frailty, which is now established to be an important determinant of mortality in patients with end-stage liver disease<sup>[1]</sup>.

We acknowledge several limitations to our study. Since this was a cross-sectional study, we were only able to ascertain beta-blocker use at a single visit, but recognize that beta-blocker prescription could have changed during the course of the patient’s time on the waitlist. Adherence to beta-blocker therapy could not be verified, but the median heart rate was significantly lower in the beta-blocker users. Inclusion of only outpatients with MELD scores  $\geq 12$  limits the study’s generalizability to the liver transplant population as a whole, but we expect those with MELD scores  $< 12$  to be less frail and therefore, even less affected by beta-blocker use. Lastly, given the observational nature of this study, we could not conclude the absence of causality between non-selective beta-blockers and physical frailty.

Despite these limitations, our data provide important data for clinicians who manage patients with cirrhosis and portal hypertension. This study is, to our knowledge, the first to investigate the association between commonly reported beta-blocker side effects of fatigue and weakness on physical frailty, of which fatigue and weakness are major components. The lack of any clinically meaningful difference in rates of physical frailty in addition to the strong association with mortality benefit of non-selective beta-blockers (in this study and in others<sup>[9,12,13]</sup>) provide reassuring evidence in support of non-selective beta-blocker use when indicated.

## ARTICLE HIGHLIGHTS

### Research background

Patients with cirrhosis are vulnerable to developing physical frailty, and it is becoming increasingly apparent that frailty predicts poor waitlist mortality. Frequently reported side effects of beta-blockers include weakness and fatigue, which overlap with aspects of frailty.

### Research motivation

There are an increasing number of studies that indicate physical frailty as a predictor of mortality in patients awaiting liver transplant. Given that beta-blockers have commonly reported side effects of fatigue and weakness, it is possible that they could accelerate physical frailty.

### Research objectives

The objective of this study was to determine the association between beta-blocker use with physical frailty, exhaustion, physical activity and mortality in patients with cirrhosis.

### Research methods

Three-hundred-forty-four patients with cirrhosis underwent physical frailty testing using the Liver Frailty Index, which includes chair stands, grip strength and balance testing. Data was also collected on self-reported assessments of exhaustion and amount of physical activity. Data on beta-blocker usage was obtained from chart review. Both univariable and multivariable logistic regression were performed to determine if there was an association with

physical frailty and beta-blocker use.

### Research results

Fifty three percent of the patients were prescribed a beta-blocker. In both univariable and multivariable models, beta-blocker users did not have increased odds of physical frailty (as defined by LFI  $\geq$  4.5), higher rates of exhaustion, or lower physical activity levels. Patients on beta-blockers had a 45% reduction in odds of waitlist mortality compared to patients not on beta-blockers.

### Research conclusions

Our study demonstrates that in patients with cirrhosis, beta-blocker use is not associated with physical frailty, exhaustion, or lower physical activity. Furthermore, our study confirms the survival benefits of beta-blocker use.

### Research perspectives

Taken together, our findings suggest that there is no association with beta-blocker use and physical frailty, and that concerns about side effects should not prevent their use when indicated. Since this is an observational study, future studies will be needed to conclude the absence of causality.

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