Title

Nonselective beta-blockers may lead to stage 2 acute kidney injury and waitlist mortality in child class C cirrhosis

Journal

Hepatology Communications, 7(10)

ISSN

2471-254X

Authors

Lai, Mason

Fenton, Cynthia

Ge, Jin

et al.

Publication Date

2023

DOI

10.1097/hc9.0000000000000255

Peer reviewed

Received: 24 May 2023 | Accepted: 21 July 2023

DOI: 10.1097/HC9.0000000000000255

ORIGINAL ARTICLE

OPEN

Nonselective beta-blockers may lead to stage 2 acute kidney injury and waitlist mortality in child class C cirrhosis

Mason Lai | **Cynthia Fenton** | **Jin Ge** | **Jessica Rubin** | **Jennifer C. Lai** | **Giuseppe Cullaro**

Department of Medicine, University of California-San Francisco, San Francisco, California, USA

Correspondence
Giuseppe Cullaro, 513 Parnassus Avenue, UCSF Box 0538, San Francisco, CA 94143, USA.
Email: Giuseppe.cullaro@ucsf.edu

Abstract

Background and Aims: Nonselective beta-blockers (NSBB) protect patients with compensated cirrhosis; however, it is unclear if NSBB is associated with acute kidney injury (AKI) in patients with decompensated cirrhosis. We aimed to determine if the use of NSBB was associated with an increased risk of stage II AKI or greater and waitlist mortality (WLM) among patients with decompensated cirrhosis awaiting liver transplant stratified by cirrhosis severity.

Methods: Included were 1816 outpatients listed for liver transplantation at UCSF from June 2012 to April 2022. Our primary outcome was stage 2 AKI (>200% increase in serum creatinine). Our secondary outcome was WLM (all-cause mortality). Our primary exposure was the use of any NSBB derived using natural language processing of clinical notes. Multivariable Cox proportional hazards models with time-dependent variables were used to determine the HR of NSBB use on stage 2 AKI and WLM, stratified by Child-Pugh Score.

Results: The average age of the cohort was 58 years old, with 35% identifying as female. In multivariable time-dependent models, NSBB use was associated with 1.53 × (95 CI 1.19–1.97) the hazard of stage 2 AKI in the cohort overall and 1.80 × (95 CI 1.26–2.57) among those with Child C cirrhosis, respectively. Similarly, NSBB use was associated with 1.30 × (95 CI 1.07–1.59) and 1.45 × (95 CI 1.03–2.03) the hazard of WLM, overall and in Child C, respectively. NSBB use was not significantly associated with AKI nor WLM among those with Child A.

Conclusion: NSBB use is associated with Stage 2 AKI and WLM in patients awaiting liver transplantation and Child C cirrhosis. These data suggest cautious use of NSBBs in patients in this population.

Abbreviations: ALD, alcohol-associated liver disease; AKI, acute kidney injury; BPM, beats per minute; CPS, Child-Pugh Score; FrAILT, functional assessment in liver transplantation; MAP, mean arterial pressure; MELDNa, Model for End-Stage Liver Disease with Serum Sodium; NSBB, nonselective beta-blockers; WLM, waitlist mortality.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepcommjournal.com.

INTRODUCTION

NSBB is a therapeutic cornerstone for portal hypertension in compensated cirrhosis but may increase the risk of AKI in decompensated cirrhosis. Cirrhosis is a progressive syndrome characterized by portal hypertension with multisystem consequences. Compensated cirrhosis may evolve into decompensated cirrhosis, marked by ascites, variceal bleeding, or HE. Decompensation in cirrhosis is marked by increased hepatic resistance, decreased effective arterial circulation, RAAS dysregulation, and increased portal inflow. These components comprise a vicious cycle with devastating effects.[1] The result of this cycle is hemodynamic instability, placing patients with cirrhosis at elevated risk of decompensated cirrhosis-related morbidity and mortality.

While NSBBs have been firmly established in the treatment of patients with compensated cirrhosis,[1–7] whether NSBBs confer similar benefits among decompensated cirrhosis patients is less clear. The concern is that once patients decompensate, the "therapeutic window" may close, predisposing patients to unwanted hemodynamic changes.[8] These hemodynamic changes may include a decrease in mean arterial pressure (MAP) or a blunting of cardiac function—hemodynamic changes which, in effect, may disrupt tenuous physiologic homeostasis and predispose patients with cirrhosis to disruptions in kidney perfusion, worsening of volume overload, or even death. Furthermore, patients with cirrhosis are dynamic and may experience bleeding episodes, infection, or AKI, which can affect their NSBB use. However, prior studies examining the risks of NSBB use have generally done so at a single point in time, which may not accurately reflect real-world NSBB use. Given the potential negative downstream consequences of NSBBs, we hypothesized that the utilization of NSBBs in patients with decompensated cirrhosis is associated with an increased risk of AKI and waitlist mortality. To test this hypothesis and address the gap in the literature, we used a large, fully characterized, well-established cohort of patients with cirrhosis awaiting liver transplantation to evaluate the association between NSBB and (1) Stage 2 AKI and (2) mortality, stratified by Child-Pugh Score (CPS).

METHODS

Cohort derivation

Patients listed for liver transplantation at the University of California, San Francisco, and enrolled in the Functional Assessment in Liver Transplantation (FrAILT) study were included in this analysis. The details of this cohort have been published.[9,10] Briefly, the FrAILT study included patients 18 years or older with a diagnosis of cirrhosis, an active listing for liver transplantation, and seen in the ambulatory setting. Informed consent was obtained from all participants. Individuals were excluded if (1) the patient did not speak English, Spanish, or Chinese (due to the availability of consent forms), or (2) if severe HE was present (defined by a Numbers Connection Test $\geq$ 120 s) at the time of recruitment due to concerns about the inability to provide informed consent. Individuals were excluded if renal replacement therapy was in use at the time of enrollment.

Covariates

For this study, we expanded the available data in the FrAILT cohort to include all demographic and laboratory data available in 2 electronic health records—University of California, San Francisco Medical Center's EPIC-based (Verona, WI) electronic health records retrieved through Clarity and a dedicated transplant surgery database with machine automated transfer and manual entry of clinical data, including laboratory data from non-University of California, San Francisco sources. Sociodemographic data were obtained at the time of enrollment in the FrAILT cohort. Time-varying clinical variables, such as laboratory values, were continuously updated in our dataset. Because these patients were listed for a liver transplant, they had scheduled laboratory values as follows: Model for End-Stage Liver Disease with serum Sodium (MELDNa) $<$ 20 every 90 days, if MELDNa $\geq$ 20 every 30 days, and if MELDNa $\geq$ 25 every 7 days. If participants had more than 1 serum creatinine in a 7-day period, we included only the highest serum creatinine value. We limited the MELDNa score to ranges from 6 to 40 for all analyses, as done in clinical practice and in previous studies (Based on OPTN policy as of March 1, 2023).

We used natural language processing (NLP), specifically string matching, of ambulatory hepatology and liver transplant visits to determine the following variables: ascites, HE, and NSBB use (Supplemental Table S1, http://links.lww.com/HC9/A525). Ambulatory visits were chosen to measure NSBB exposure as the patient medication lists are reconciled by medical assistants at each clinic visit. For ascites, "mild to moderate" was defined as present on physical examination but not requiring recurrent large-volume paracenteses, and "severe" was defined as requiring recurrent large-volume paracenteses. We determined the presence of HE by the presence of either lactulose or rifaximin on medication review. For NSBB use, we first identified the documentation of "propranolol", "nadolol", or "carvedilol". We then searched the 100 characters before and after the NSBB (ie, propranolol, nadolol, and carvedilol). NLP string matching was performed in R (4.2.1) using the following additional packages: "stringR"[11] and "tidyverse".[12] Our

conceptual model of variable relationships is shown in Supplemental Figure S1, http://links.lww.com/HC9/A525.

Exposure

We validated our exposure variable through the following steps: (1) We completed a McNemar test to estimate that based on a correlation between chart review and our NLP algorithm of 90%, we would have 90% power to detect a 14% difference in the sensitivity and specificity with a chart review of 150 patients at the $p < 0.05$ level. (2) We report the sensitivity, specificity, negative predictive value, and positive predictive value of our NLP algorithm in 150 randomly selected patient encounters, with corresponding CIs generated by bootstrapping. Our manual validation of NSBB use in a random subsample of 150 patients showed a sensitivity of 87% (95% CI 86–96%), specificity of 96% (95% CI 89–100%), negative predictive value of 75% (95% CI 62-86%), and a positive predictive value of 98% (95% CI 92–100%).

NSBB use was the primary exposure. NSBB use was treated as a time-dependent variable in all survival models. Given that current practice in NSBB prescription is to titrate to heart rate rather than use a fixed dose, we opted to utilize beta-blocker use as a binary variable rather than use beta-blocker dose as a continuous variable.

Stratification

To better explore the hypothesized "therapeutic window" and differences in adverse outcomes by cirrhosis severity, we stratified all our analysis by CPS Classes: A (CPS $\leq$ 6); B (CPS 7 – 9); C (CPS $\geq$ 10).

Outcome

Stage 2 AKI or greater, as defined by the International Club of Ascites, was the primary outcome. This was defined as either a $\geq$ 200% increase in serum creatinine or the initiation of renal replacement therapy within a 7-day period during follow-up.[13] We focused on more severe AKI (ie, Stage 2 AKI or greater), as these events are more clinically impactful. Our secondary outcome was all-cause mortality while on the liver transplantation waitlist.

Statistical analysis

Descriptive analyses used Wilcoxon rank sum tests and chi-square tests, as appropriate. In the cohort overall and in each CPS class, we used time-dependent Cox proportional hazards regression models to determine the associations between NSBB use and our 2 outcomes (Stage 2 AKI or greater and waitlist mortality); For each model outcome, we first conducted univariable analyses, followed by a multivariable model with an adjustment set generated using a causal approach (Supplemental Figure S1, http://links.lww.com/HC9/A525).

Analyses were completed in R ("Funny Looking Kid," version 4.2.1) and R Studio.

This study was approved by the IRB at the University of California, San Francisco.

RESULTS

Patient characteristics

Among 1816 outpatients enrolled in our cohort from June 2012 to April 2022 and followed for a median of 1.5 years (IQR 0.7–3.0), 380 patients (21%) were Child A, 723 patients were Child B (40%), and 713 (39%) patients were Child C at the time of enrollment. We demonstrate the baseline demographic data by Child class and NSBB use in Table 1. Among those who had platelet count > 100,000/μL at study enrollment, the median time to platelet count <100,000/μL was 346 days (IQR 132–1156 days).

NSBB use and NSBB user characteristics

Among enrolled participants, 813 (45%) received NSBB at 1 or more time points during follow-up. Among NSBB users, 619 (76%) received propranolol, 127 (16%) received nadolol, and 67 (8%) received carvedilol. NSBB use stratified by CPS is shown in Table 1.

NSBB use by indication is shown in Supplemental Table S2, http://links.lww.com/HC9/A525. Among participants who ever used NSBB during follow-up, the median fraction of follow-up time on NSBB was 0.78 years (IQR 0.42–0.94).

Among the NSBB users, 12 (12%) with Child A cirrhosis, 81 (25%) with Child B cirrhosis, and 78 (24%) with Child C cirrhosis had prior esophageal variceal bleeding. When stratified by the Child class, those on NSBB for secondary prophylaxis had no difference in the proportion of Stage 2 AKI or greater or waitlist mortality, compared to those on NSBB for primary prophylaxis.

Within each Child class, compared with those not receiving NSBB, those who received NSBB had significantly lower HRs (Child A: 67 vs. 72 BPM; Child B: 68 vs. 73 BPM; and Child C: 69 vs. 78 BPM; $p \leq 0.005$ for each comparison). Among those with Child A and Child B cirrhosis, there were no

TABLE 1 Clinical characteristics at baseline by child class and NSBB status

Characteristic	Child A			Child B			Child C		
	No NSBB, N = 280[a]	Any NSBB, N = 100[a]	p[b]	No NSBB, N = 403[a]	Any NSBB, N = 320[a]	p[c]	No NSBB, N = 392[a]	Any NSBB, N = 321[a]	p[c]
Sex, n (%)	—	—	0.3	—	—	0.11	—	—	0.2
Female	60 (21)	26 (26)	—	146 (37)	100 (31)	—	172 (44)	125 (39)	—
Male	220 (79)	74 (74)	—	247 (63)	219 (69)	—	220 (56)	196 (61)	—
Age (y)	64 (60, 67)	62 (59, 66)	0.12	60 (54, 64)	60 (54, 64)	0.5	57 (49, 62)	57 (50, 62)	0.4
Race, n (%)	—	—	0.018	—	—	0.4	—	—	0.2
Non-White	88 (31)	19 (19)	—	68 (17)	47 (15)	—	48 (12)	29 (9.0)	—
White	192 (69)	81 (81)	—	325 (83)	272 (85)	—	344 (88)	292 (91)	—
Etiology, n (%)	—	—	0.011	—	—	0.2	—	—	50
ALD	21 (7.5)	10 (10)	—	74 (19)	63 (20)	—	128 (33)	92 (29)	—
HCV	165 (59)	60 (60)	—	150 (38)	142 (45)	—	94 (24)	107 (33)	—
NAFL	14 (5.0)	13 (13)	—	77 (20)	51 (16)	—	84 (21)	57 (18)	—
Other	80 (29)	17 (17)	—	92 (23)	63 (20)	—	86 (22)	65 (20)	—
HCC, n (%)	249 (89)	76 (76)	0.002	153 (39)	127 (40)	0.8	51 (13)	61 (19)	0.029
Body mass index (kg/m2)	26.6 (24.2, 31.3)	27.2 (24.7, 30.7)	0.4	28.1 (24.3, 32.2)	28.6 (25.6, 33.0)	0.027	28.0 (24.5, 32.0)	29.3 (25.5, 33.8)	0.015
Mean Arterial Pressure (mmHg)	96 (87, 104)	93 (87, 100)	0.13	86 (80, 96)	86 (78, 93)	0.076	82 (76, 92)	82 (74, 90)	0.3
Heart rate (BPM)	72 (62, 79)	67 (61, 74)	0.005	73 (66, 83)	68 (61, 76)	<0.001	78 (70, 88)	69 (62, 79)	<0.001
Ascites Status, n (%)	—	—	<0.001	—	—	0.003	—	—	0.058
None	260 (93)	78 (78)	—	122 (31)	69 (22)	—	27 (6.9)	10 (3.1)	—
Mild/Moderate	20 (7.1)	22 (22)	—	199 (51)	202 (63)	—	191 (49)	172 (54)	—
Severe	0 (0)	0 (0)	—	72 (18)	48 (15)	—	174 (44)	139 (43)	—
HE, n (%)	—	—	0.13	—	—	0.001	—	—	0.7
None	260 (93)	88 (88)	—	157 (40)	91 (29)	—	31 (7.9)	23 (7.2)	—
Present	20 (7.1)	12 (12)	—	234 (60)	228 (71)	—	361 (92)	298 (93)	—
MELDNa	8.5 (7.5, 9.7)	9.4 (8.5, 11.1)	<0.001	15.3 (10.9, 18.5)	15.3 (11.5, 17.6)	0.6	21.5 (18.0, 25.1)	19.6 (16.8, 22.7)	<0.001
Albumin (g/dL)	3.9 (3.6, 4.2)	3.8 (3.5, 4.0)	0.002	3.2 (2.9, 3.5)	3.2 (2.9, 3.5)	0.5	2.7 (2.3, 3.0)	2.7 (2.4, 3.1)	0.3

[a]n (%); Median (IQR).
[b]Pearson's chi-squared test; Wilcoxon rank sum test; Fisher's exact test.
[c]Pearson's chi-squared test; Wilcoxon rank sum test.
Abbreviations: ALD, alcohol-associated liver disease; BPM, beats per minute; MELDNa, Model for End-Stage Liver Disease with serum sodium; NSBB, nonselective beta-blocker.

differences in MELDNa scores between those who did and did not receive NSBB ($p > 0.05$ for both). However, among those with Child C cirrhosis, those who received NSBB had significantly lower MELDNa scores (20 vs. 22, $p < 0.001$) than those not receiving NSBB.

NSBB use and Stage 2 AKI or greater

Among 1816 patients with decompensated cirrhosis, 291 experienced stage 2 AKI or greater. In time-dependent Cox regression models, we found a significant association between NSBB use and Stage 2 AKI (HR 1.57, 95 CI 1.24–1.99). In models additionally adjusting for confounders, this association between NSBB use and Stage 2 AKI remained significant (HR 1.53, 1.19–1.97).

To better characterize the association between NSBB use and Stage 2 AKI, we performed analyses stratified by CPS. Among 380 patients with Child A cirrhosis, 26 (7%) experienced Stage 2 AKI or greater. In patients with Child A cirrhosis, we found that in time-dependent Cox regression models, NSBB use and Stage 2 AKI were not significantly associated in univariate analyses, as well as models adjusting for confounders (Figure 1).

Among 723 patients with Child B cirrhosis, 120 (17%) experienced Stage 2 AKI or greater. In patients with Child B cirrhosis, we did not find a significant association in univariate models between NSBB use and stage 2 AKI, nor in multivariate models evaluating for confounders (Figure 1).

Among 713 patients with Child C cirrhosis, 152 (21%) experienced Stage 2 AKI. In patients with Child C cirrhosis, we did find a significant association in univariate models between NSBB use and stage 2 AKI (HR 1.62, 95

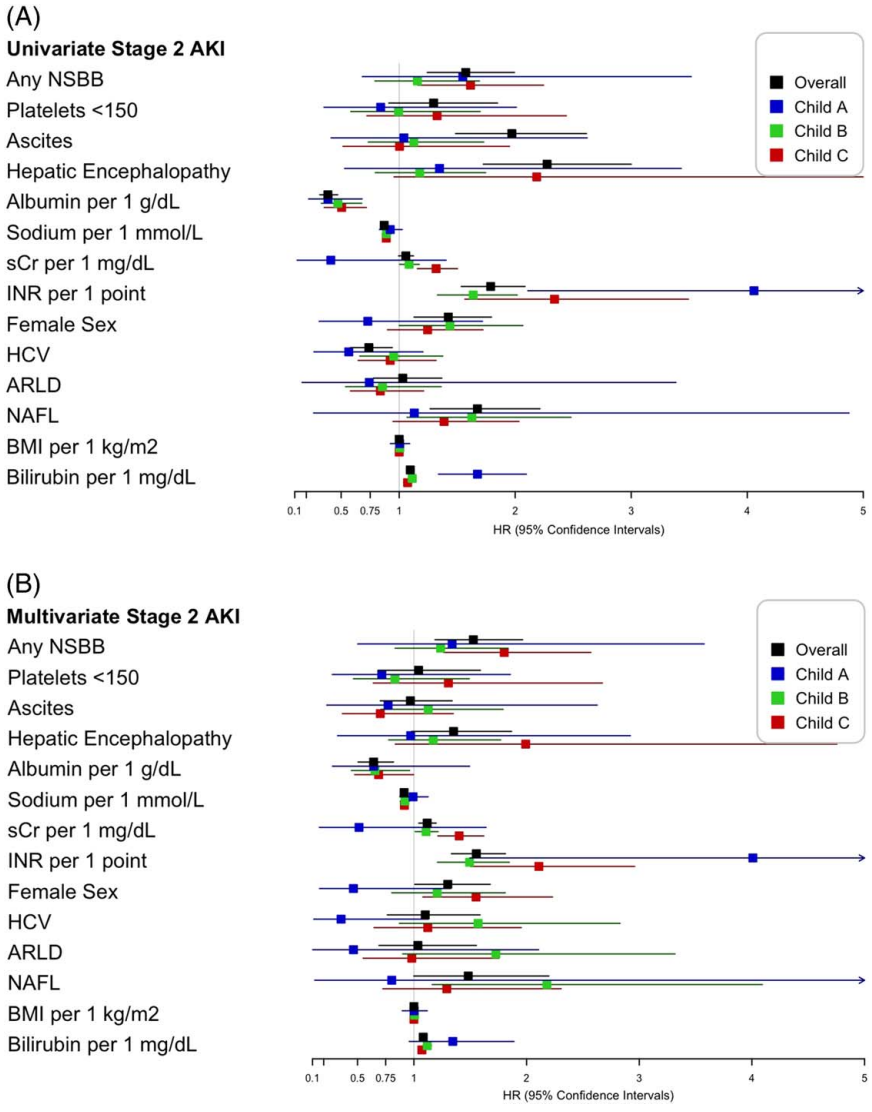

FIGURE 1 Forest plot of univariable and multivariable factors associated with stage 2 aki among patients with decompensated cirrhosis, stratified by Child-Pugh Score. Cox Proportional Hazards models were used. Abbreviations: ALD, alcohol-associated liver disease; MELDNa, Model for End-Stage Liver Disease with serum sodium; NSBB, nonselective beta-blocker.

CI 1.16–2.24). Similarly, in adjusted models evaluating for confounders, we found that NSBB use was associated with 1.80 × the hazard of developing Stage 2 AKI during follow-up (aHR 1.80, 95 CI 1.26–2.57) (Figure 1).

NSBB use and waitlist mortality

In our cohort of patients with decompensated cirrhosis, 465 (26%) died or were removed from the waitlist due to sickness during follow-up. In time-dependent Cox regression models, NSBB use and waitlist mortality were associated (HR 1.40, 95 CI 1.17–1.67). Similarly, in multivariate models adjusting for confounders, NSBB and waitlist mortality remained (aHR 1.30, 95 CI 1.07–1.59).

Among those with Child A cirrhosis, 89 (23%) died or were removed from the waitlist due to sickness during follow-up. In time-dependent Cox regression models among those with Child A cirrhosis, we did not find a significant association in univariable models between NSBB use and waitlist mortality (Figure 2). Similarly, in multivariable models, NSBB use was not associated with waitlist mortality.

Among those with Child B cirrhosis, 212 (30%) died or were removed from the waitlist due to sickness during follow-up. In time-dependent Cox regression models, NSBB use and waitlist mortality were significantly associated (HR 1.56, 95 CI 1.20–2.04). Similarly, in adjusted models evaluating for confounders and the propensity to be on NSBB, we found that NSBB use was associated with a 1.38 × the hazard of waitlist mortality during follow-up (aHR 1.38, 95 CI 1.04–1.85) (Figure 2).

Among those with Child C cirrhosis, 164 (23%) died or were removed from the waitlist for sickness during follow-up. In time-dependent Cox regression models, NSBB use and waitlist mortality were directionally associated, although this association did not reach statistical significance (HR 1.34, 95 CI 0.98–1.81). In adjusted models evaluating for confounders, we found that NSBB use was associated with 1.45 × the hazard of waitlist mortality during follow-up (aHR 1.45, 95 CI 1.03–2.03, Figure 2).

Sensitivity analyses: Interaction

To determine if the effect modification of NSBB use on AKI by Child-Pugh Class was present, we tested for interaction between NSBB use and Child-Pugh Class, which was not significant. Similarly, interaction testing between NSBB use on mortality by Child-Pugh Class was not significant. However, we were underpowered to test interaction for each of these outcomes. We additionally repeated our analyses when stratified by ascites severity, shown in Supplemental Figures S2 and S3, http://links.lww.com/HC9/A525.

DISCUSSION

In the large, well-characterized FrAILT cohort of 1816 patients with decompensated cirrhosis listed for liver transplantation, we showed the use of NSBB was associated with stage 2 AKI or greater and waitlist mortality among those with decompensated cirrhosis. Our findings persisted even after adjusting for an expansive set of confounders. These data demonstrate that while NSBB use may be warranted among patients with compensated cirrhosis, their use is not without harm among those with decompensated cirrhosis. In particular, much of the effect in this cohort of patients with decompensated cirrhosis appeared to be driven by those with Child Class C cirrhosis. This study provides further support for the "therapeutic window" in cirrhosis, specifically that NSBB use is relatively safe in decompensated patients with Child A cirrhosis but should be used with caution in patients with more severe cirrhosis.

Identification of medication utilization in cohort studies is difficult. To our knowledge, this is one of the first studies to apply NLP to unstructured clinical notes to determine whether a patient with cirrhosis was on NSBB. Most studies either require the manual entry of medication utilization—a time-consuming process that makes it difficult to continuously update—or requires the incorporation of claims databases (eg, Optum), which can be prohibitively expensive and not always available for all subjects.[14] For these reasons, in this study, we utilized natural language processing of clinic notes to identify the utilization of NSBBs in a diverse cohort of patients with decompensated cirrhosis. Our methodology was accurate, with a sensitivity of 87%, a specificity of 96%, a negative predictive value of 75%, and a positive predictive value of 98%. Although our methodology does not confirm medication adherence, our data demonstrate that for each Child class, those on NSBBs had significantly lower HRs—a finding that supports the validity of our methodology. We believe the utilization of these novel techniques will enable the real-world validation of current interventions outside of clinical trials.

When and in whom to use NSBBs is a topic of active discussion, with the boundaries of the "therapeutic window" remaining unclear.[15–17] One hypothesized complication of NSBB use outside of the "therapeutic window" is AKI.[8,18] Physiologically, this is hypothesized as the consequence of NSBBs disrupting compensatory hemodynamic mechanisms.[17] Previous studies examining NSBBs and AKI include patients with compensated cirrhosis or are limited by small sample sizes.[17,19–22] Therefore, we leveraged a large cohort of patients with decompensated cirrhosis to assess this association between NSBB use and AKI in decompensated cirrhosis overall and stratified by CPS. In fact, we highlight that NSBB use was associated with 1.5 × the risk of Stage 2 AKI overall and 1.8 × the risk of

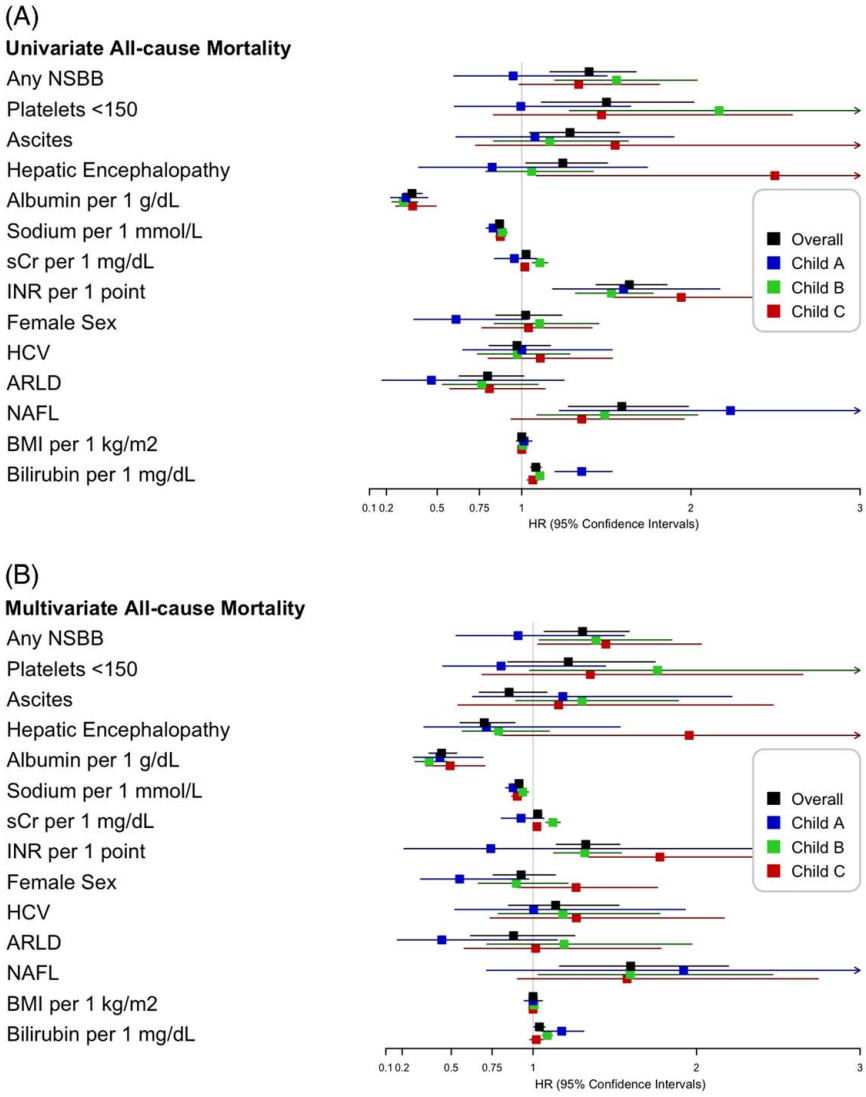

FIGURE 2 Forest Plot of Univariable and Multivariable Factors Associated with Waitlist Mortality Among Patients with Decompensated Cirrhosis, Stratified by Child-Pugh Score. Cox Proportional Hazards models were used. Abbreviations: ALD, alcohol-associated liver disease; MELDNa, Model for End-Stage Liver Disease with serum sodium; NSBB, nonselective beta-blocker.

Stage 2 AKI, among those with Child C cirrhosis. These are meaningful associations, as stage 2 AKI or greater is a serious outcome among decompensated cirrhosis patients with important clinical implications. Finally, although we hypothesized that NSBBs would disrupt compensatory hemodynamic mechanisms, we did not find any significant interactions between NSBB use and either HR or MAP—a finding that goes against this hypothesis but may be a consequence of HR and MAP measurements being limited to in-person, outpatient visits and therefore may be too infrequent to fully quantify this interaction.

Stage 2 AKI represents just 1 complication of decompensated cirrhosis that could lead to mortality[8]; therefore, we also investigated the association between NSBB use and waitlist mortality. Prior literature on NSBBs and mortality shows considerable heterogeneity in both patients and study quality[23,24]; it remains unclear how NSBB might affect waitlist mortality in decompensated cirrhosis. In the present study, we found that NSBB use was associated with increased mortality in decompensated cirrhosis (aHR 1.3), and specifically only among those with Child B and Child C cirrhosis was NSBB use associated with increased mortality (aHR 1.4, 1.5, respectively) even after adjusting for covariates. Furthermore, when stratified by the Child class, those who were on NSBB appeared to be equally as decompensated (by MELDNa) as those, not on NSBB. In fact, those with Child C cirrhosis on NSBB had significantly lower MELDNa scores as compared with those not on NSBB. We believe that should there be residual confounding, this confounding should bias our results to the null, as NSBBs would be less utilized in the sicker (ie, more at-risk) population. Collectively, we believe these data highlight that NSBB use in patients

with Child B and Child C cirrhosis is associated with higher waitlist mortality.

This study has several limitations. First, the cohort was observational in nature and is thus subject to residual confounding—future clinical trials of NSBB utilization should focus on defining the benefits (eg, preventing rebleeding) and potential harms (eg, AKI, mortality) among patients with decompensated cirrhosis for either primary or secondary prophylaxis. Second, although the use of natural language processing to derive our exposure had excellent sensitivity and specificity, the results of the study are subject to a small degree of exposure measurement bias. Nonetheless, given the highly specific results of our methodology, we suspect this measurement bias would bias our results towards the null—patients on NSBB would be measured as not being on NSBB and therefore lead to an increase in the outcomes in the control groups. Third, our cohort had a high proportion of individuals using propranolol, and the findings of this study may not generalize to other NSBB agents such as carvedilol. Fourth, we did not have data on variceal bleeding during follow-up. We used platelet count as a proxy of portal hypertension and varices but acknowledge that this is not an ideal marker and may be subject to residual confounding. Finally, although we did not find differences in our outcomes by indication (ie, primary vs. secondary prophylaxis), we may not have been powered to detect an effect by indication.

Despite these limitations, our findings that the use of NSBB is independently associated with stage 2 AKI or greater and waitlist mortality among patients with decompensated cirrhosis listed for liver transplant is significant. Our data suggests that clinicians should exercise caution when considering the use of NSBBs in patients with decompensated cirrhosis awaiting a liver transplant, particularly those with Child C cirrhosis.

AUTHOR CONTRIBUTIONS

Mason Lai: Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Cynthia Fenton: Acquisition of the data; interpretation of data; preparation of manuscript, including final approval for publication. Jin Ge: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; study supervision. Jessica Rubin: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; study supervision. Jennifer C. Lai: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; study supervision. Giuseppe Cullaro: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; study supervision

FUNDING INFORMATION

This study was funded by NIH R01AG059183 (Jennifer C. Lai), the UCSF Liver Center P30 DK026743 (Giuseppe Cullaro, Jennifer C. Lai, Jin Ge, Jessica Rubin), NIH K23DK131278 (Giuseppe Cullaro), NIH KL2TR001870 (Jin Ge and Jessica Rubin), American Society of Transplantation LICOP Research Award (Jin Ge), the American Association for the Study of Liver Disease Clinical, Translational, and Outcomes Research Award (Giuseppe Cullaro), and NIH 2TL1TR001871-06 (Mason Lai). These funding agencies played no role in the analysis of the data or the preparation of this manuscript.

CONFLICTS OF INTEREST

Giuseppe Cullaro: Research Support—Mallinckrodt Pharmaceuticals; Site Investigator—Ocelot Pharmaceuticals; Advisory Board—Ocelot Pharmaceuticals; Jennifer C. Lai: Consultant—GenFit Corp; Advisory Board—Novo Nordisk; Research support—Gore Therapeutics; Site investigator—Lipocine; Jin Ge: Research Support—Merck and Co. The remaining authors have no conflicts to report.

ORCID

Mason Lai https://orcid.org/0000–0001–9501–1199
Jin Ge https://orcid.org/0000–0003–1574–1525
Jessica Rubin https://orcid.org/0000–0003–2105–1256
Jennifer C. Lai https://orcid.org/0000–0003–2092–6380
Giuseppe Cullaro https://orcid.org/0000–0002–2935–0245

REFERENCES

1. Rabiee A, Garcia-Tsao G, Tapper EB. Nonselective beta-blockers in portal hypertension: Why, When, and How? Clin Liver Dis. 2022;19:118–23.
2. Rodrigues SG, Mendoza YP, Bosch J. Beta-blockers in cirrhosis: Evidence-based indications and limitations. JHEP Rep. 2020;2: 100063.
3. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: A controlled study. N Engl J Med. 1981;305:1371–4.
4. Pascal JP, Cales P. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. N Engl J Med. 1987;317: 856–61.
5. Pérez-Ayuso RM, Piqué JM, Bosch J, Panés J, González A, Pérez R, et al. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. Lancet. 1991;337:1431–4.

6. Villanueva C, Torres F, Sarin SK, Shah HA, Tripathi D, Brujats A, et al. Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. J Hepatol. 2022;77:1014–25.
7. Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, 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;393:1597–608.
8. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII– Renewing consensus in portal hypertension. J Hepatol. 2022;76:959–74.
9. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant. 2014;14:1870–9.
10. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology. 2017;66:564–74.
11. Wickham H Stringr: Simple, Consistent Wrappers for Common String Operations. 2022.
12. Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the Tidyverse. J Open Source Softw. 2019;4:1686.
13. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. Gut. 2015;64:531–7.
14. Pevnick JM, Palmer KA, Shane R, Wu CN, Bell DS, Diaz F, et al. Potential benefit of electronic pharmacy claims data to prevent medication history errors and resultant inpatient order errors. J Am Med Inform Assoc. 2016;23:942–50.
15. Yoon KT, Liu H, Lee SS. β-blockers in advanced cirrhosis: More friend than enemy. Clin Mol Hepatol. 2021;27:425–36.
16. Ge PS, Runyon BA. The changing role of beta-blocker therapy in patients with cirrhosis. J Hepatol. 2014;60:643–53.
17. Kim SG, Larson JJ, Lee JS, Therneau TM, Kim WR. Beneficial and harmful effects of nonselective beta blockade on acute kidney injury in liver transplant candidates. Liver Transpl. 2017;23:733–40.
18. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.
19. Scheiner B, Parada-Rodriguez D, Bucsics T, Schwabl P, Mandorfer M, Pfisterer N, et al. Non-selective beta-blocker treatment does not impact on kidney function in cirrhotic patients with varices. Scand J Gastroenterol. 2017;52:1008–15.
20. Li T-H, Liu C-W, Huang C-C, Tsai Y-L, Huang S-F, Yang Y-Y, et al. Non-selective beta-blockers decrease infection, acute kidney injury episodes, and ameliorate sarcopenic changes in patients with cirrhosis: A propensity-score matching tertiary-center cohort study. J Clin Med. 2021;10:2244.
21. Premkumar M, Rangegowda D, Vyas T, Khumuckham JS, Shasthry SM, Thomas SS, et al. Carvedilol combined with ivabradine improves left ventricular diastolic dysfunction, clinical progression, and survival in cirrhosis. J Clin Gastroenterol. 2020;54:561–8.
22. Ngwa T, Orman E, Gomez EV, Vuppalanchi R, Kubal C, Chalasani N, et al. Non-selective beta blocker use is associated with improved short-term survival in patients with cirrhosis referred for liver transplantation. BMC Gastroenterol. 2020;20:4.
23. Wong RJ, Robinson A, Ginzberg D, Gomes C, Liu B, Bhuket T. Assessing the safety of beta-blocker therapy in cirrhosis patients with ascites: A meta-analysis. Liver Int. 2019;39:1080–8.
24. Chirapongsathorn S, Valentin N, Alahdab F, Krittanawong C, Erwin PJ, Murad MH, et al. Nonselective β-blockers and survival in patients with cirrhosis and ascites: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14:1096–1104.e1099.

How to cite this article: Lai M, Fenton C, Ge J, Rubin J, Lai JC, Cullaro G. Nonselective beta-blockers may lead to stage 2 acute kidney injury and waitlist mortality in child class C cirrhosis. Hepatol Commun. 2023;7:e0255. https://doi.org/10.1097/HC9.0000000000000255