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# Frailty, Psychoactive Medications, and Cognitive Dysfunction Are Associated With Poor Patient-Reported Outcomes in Cirrhosis

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**Cirrhosis is associated with disabling symptoms and diminished health-related quality of life (HRQOL). However, for patients with compensated disease, data are limited regarding associations with poor patient-reported outcomes (PROs). We prospectively enrolled 300 patients with cirrhosis and portal hypertension without a history of hepatic encephalopathy (HE) and reviewed medical and pharmacy records. We characterized determinants of PROs using the 8-item Short-Form Health Survey (SF-8) scale (0-100) and sleep quality using the Pittsburgh Sleep Quality Index (PSQI; poor sleep >5). Disability and frailty measures were assessed using activities of daily living (ADLs), falls, hand-grip, and chair-stands. Cognitive function was measured using weighted-lures from the Inhibitory Control Test (ICT). The median age of our cohort was 60 (interquartile range [IQR], 52-66) years, 56.3% were male, and 70% Child class A. All patients had portal hypertension, 76% had varices, and 41% had a history of ascites (predominantly well controlled). The median Model for End-Stage Liver Disease with Sodium (MELD-Na) score was 9 (IQR, 7-13). The overall median SF-8 was 70 (IQR, 54-86). Multivariate analysis showed that after adjusting for age, sex, education, and MELD-Na, performance on chair-stands (9.28 HRQOL points [95% confidence interval {CI}, 4.76-13.8] per 10-stands), ADL dependence (–6.06 [–10.8 to –1.36]), opiate use (–5.01 [–7.84 to –2.19]), benzodiazepine use (–3.50 [–6.58 to –0.42]), and ICT performance (–0.10 [–0.20 to 0.001] per weighted-lure) were significantly associated with HRQOL. Among patients completing the ICT, poor HRQOL (score <50) was significantly associated with chair-stands (odds ratio [OR] per 10-stands, 0.24; 95% CI [0.11-0.56]) and weighted lures (OR per weighted-lure, 1.01 [1.00-1.03]). Poor sleep quality was associated with opiate use (OR, 2.85 [1.11-7.29]) and lures (OR per-lure, 1.03 [1.00-1.05]). *Conclusion:* Disability, chair-stand performance, cognitive dysfunction, as well as psychoactive medication use are significantly associated with PROs in patients with clinically stable cirrhosis. (Hepatology 2019;69:1676-1685).**

Cirrhosis is the final common pathway for most chronic liver diseases.[1] The majority of the >630,000 patients with compensated cirrhosis in the United States live more than a decade after diagnosis making compensated cirrhosis a chronic condition.[2] Mortality markedly increases with onset of complications such as ascites, variceal hemorrhage, and hepatic encephalopathy (HE). In addition to clinical

*Abbreviations: ADL, activities of daily living; CCI, Charlson Comorbidity Index; CI, confidence interval; HE, hepatic encephalopathy; HRQOL, health-related quality of life; ICT, Inhibitory Control Test; INR, international normalized ratio; IQR, interquartile range; MELD-Na, Model for End-Stage Liver Disease with Sodium; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PROs, patient-reported outcomes; PSQI, Pittsburgh Sleep Quality Index; SF-8, the 8-item Short-Form Health Survey.*

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decompensations, cirrhosis is also associated with poor patient-reported outcomes (PROs) such as poor sleep and diminished health-related quality of life (HRQOL). We recently reviewed the determinants of PROs in cirrhosis.[3] Like others, we found that liver disease severity, particularly HE, is the principal driver of symptoms and poor HRQOL.[4-8] Adequate control of cirrhosis complications is therefore crucial to improving PROs.[6] Less is known, however, regarding the determinants of, and targets for, improvements of PROs among the vast majority of patients with cirrhosis who are compensated.

In order to study the incidence and predictive factors of overt HE and test interventions that might improve PROs in patients with cirrhosis, we enrolled 300 patients with cirrhosis and portal hypertension but no previous HE to characterize the determinants of their PROs in search of potentially modifiable factors. *A priori*, we were interested in psychoactive medications and frailty. Psychoactive medications are frequently used, have unique adverse effects in patients with cirrhosis,[9] and can often be substituted for equally effective alternative therapies that do not have the sedating side effects.[10-12] Indeed, in a nationally representative study of patients with noncancer chronic pain propensity matched for opiate use, opiates were not associated with improved pain or significantly different PROs.[13] Similarly, frailty is also common among patients with cirrhosis, associated with poor PROs, and in some patients may be reversed with nutrition and physical therapy.[14-17]

# Materials and Methods

We prospectively enrolled 300 subjects from the Hepatology subspecialty clinic of the University of Michigan Health System from July 2016 to April 2018. Patients were identified by a manual search of clinical schedules for all adults aged ≥18 years with a diagnosis of cirrhosis and portal hypertension based on clinical, histological, and radiographic data. In the absence of a liver biopsy, patients had to meet at least two of the following criteria: imaging findings of cirrhosis (cirrhotic appearing liver, splenomegaly, varices, or ascites), transient elastography >13 kPa, aspartate aminotransferase/platelet ratio index >2.0, and endoscopy with presence of esophageal varices. Presence of portal hypertension was defined by at least one of the following: ascites, hydrothorax, varices, or history of variceal hemorrhage; platelet count ≤80 K (in the absence of hematological causes of thrombocytopenia). We excluded all patients with Child C cirrhosis, a current or past history of overt HE (history of hospitalization for HE, current lactulose, or rifaximin prescription), non-English-speaking, estimated life expectancy <12 months, pregnancy, severe mobility impairment (e.g., hemiparesis), severe cognitive impairment (including overt HE), previous liver transplantation, or history of transjugular intrahepatic portosystemic shunt placement. This study utilizes baseline assessment of patients enrolled in a longitudinal cohort study aimed to determine incidence and predictors of overt HE. As such, patients with overt HE at enrollment were excluded. We included patients of all etiologies. All patients with hepatitis C–related cirrhosis had achieved sustained virologic response at time of enrollment. This study was approved by the University of Michigan Health System Institutional Review Board (Ann Arbor, MI), and all subjects provided written informed consent.

## SCREENING AND RECRUITMENT

Overall, 814 patients were eligible, 360 were not recruited because of being missed in clinic or not

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attending scheduled visits, 150 were approached but declined participation (66 were interested but did not have time to complete the study procedures, 58 refused, and 26 were found to be ineligible because of a new diagnosis of HE ascertained by a hepatologist during their clinic visit), and 4 were enrolled in error because of a remote history of HE.

## OUTCOMES

The primary outcome was HRQOL as measured by the the 8-item Short-Form Health Survey (SF-8). Each patient's HRQOL was denoted by a summary score that was an average of all domains (see Supporting Methods). The advantage of the SF-8 over the the 36-Item Short Form Health Survey is that it is shorter, and it has been studied in patients with chronic liver disease.[18-20] We evaluated absolute HRQOL score (0-100, scored according to RAND methods[21]) and dichotomy of scores into satisfactory and poor HRQOL defined as score <50.[22]

Sleep quality was evaluated as a secondary outcome. All patients completed the Pittsburgh Sleep Quality Index (PSQI), a widely validated tool.[23] The PSQI has been extensively studied in patients with cirrhosis.[8,24] It is strongly correlated with HRQOL and depression (patients with depression have similar HRQOL scores as those with sleep disorders[23]), in part because the PSQI measures symptoms of poor HRQOL and depression (i.e., pain, anxiety, and enthusiasm) and also because poor sleep leads to poor HRQOL. The PSQI has a range of 0-21 with scores >5 considered to be consistent with poor sleep.[23]

## EXPOSURES

An interview was conducted at the time of enrollment to collect data regarding demographics, clinical history, current daily-use medications, and comorbidities (Charlson Comorbidity Index [CCI][25]). Alcohol use over the previous 12 months was recorded using a validated questionnaire.[26] Alcohol abuse was defined by binge drinking (>5 drinks in 2 hours, >4 for women) or chronic use >7 or >14 drinks/week for women and men, respectively. Medication lists were reconciled at the time of the visit. Chronic medication use was defined as >90 days of use. We specified a distinction between tricyclic antidepressants and conventional antidepressants, because the indication for these medication classes typically differ. Severity of liver disease was assessed using the Child classification and Model for End-Stage Liver Disease with Sodium (MELD-Na).

Functional disability was assessed by the Katz Index of Independence in Activities of Daily Living (ADLs).[27] All patients were questioned about any history of falls over the previous 6 months. A physical frailty assessment was performed using two tests. Hand-grip strength was evaluated using a hand-held dynamometer; patients were asked to squeeze the device three times with their dominant hand. The force of each squeeze was recorded and the best result retained for analysis. Frail performance was defined with respect to sex and body mass index (Supporting Methods).[16] The number of chair-stands (repeatedly rising from a seated position to standing and sitting again) performed within 30 seconds was also assessed. Because of lack of standard definitions, frail performance was defined as a t-score <–1.0 (in this case, <5 chair-stands in 30 seconds), consistent with the definition used by Lai et al.[16]

Cognitive testing was performed using the Inhibitory Control Test (ICT), a validated, free-to-use, computerized test developed by Bajaj et al., which takes 10-15 minutes to complete.[28] The subject is asked to respond to cues as they are flashed on a computer screen (see example in the Supporting Information). The number of incorrect responses (called "lures") is automatically tabulated by the computer program to determine the test results. As established by Amodio et al.,[29] we also adjusted the lures for the number of correct responses (called "targets"). Weighted-lures are calculated as follows: lures/(proportion of targets met$^2$); Amodio et al. showed that a cutoff of 24 weighted-lures was associated with minimal HE by psychometric testing.

## STATISTICAL ANALYSES

Comparisons of continuous variables were performed using the Student *t* test and Wilcoxon rank-sums tests for parametric and nonparametric variables, respectively. Categorical variables were compared using a chi-squared test. To evaluate the primary outcome, we performed linear regression. We also performed a logistic regression for dichotomous HRQOL (<50 as poor) and the secondary outcome (PSQI >5). Univariable associations with *P* values <0.05

were included in multivariable regressions. Given the importance of age, sex, and MELD-Na in both quality-of-life estimates and the interpretation of many covariates (e.g., hand-grip), these variables were included in all multivariable models. An estimate of model performance was provided using the coefficient of determination (or $R^2$ value), a measure of goodness of fit that ranges from 0 to 1 (perfect fit). Many patients could not complete the ICT, limiting multivariable regressions that include cognitive performance. Rather than impute missing values, we performed sensitivity analyses for our regressions omitting ICT performance. Finally, we re-evaluated model estimates in clinically relevant subgroups, namely patients with compensated (Child A) cirrhosis, past/current ascites or diuretic use, cured hepatitis C virus, those without a history of alcohol abuse, and those without prescriptions for opiates or benzodiazepines. The sample size of 300 was determined for the primary outcomes of our longitudinal study aimed to determine predictors of incident overt HE. Power calculation was not performed for the current analysis on PROs at enrollment and associated factors. All analyses were performed using JMP Pro software (Version 13; SAS Institute Inc., Cary, NC).

# Results

## DEMOGRAPHICS AND CLINICAL FACTORS

Characteristics of our 300 enrolled patients are delineated in Table 1. Median age was 60 years, 56% were male, median years of education was 14, 70% were Child class A, and median MELD-Na score was 9. All patients had portal hypertension, including 76% with varices, 41% with a history of ascites (10% requiring paracentesis), and 37% with thrombocytopenia (PLT <80,000).

## FRAILTY AND COGNITIVE FUNCTION

Most patients (91%) were able to carry out all their ADLs independently. Compared to men, women had significantly lower hand-grip (22.8 ± 7.3 vs. 38.5 ± 12.4 kg; $P < 0.0001$), but not chair-stands (10.0 ± 5.4 vs. 9.9 ± 5.5; $P = 0.87$). Proportion of women and men with a history of falls within the last 6 months was similar (32 [24%] vs. 33 [20%]; $P = 0.33$). Ninety-one (34%) patients had impaired cognitive function based

**TABLE 1. Characteristics of the 300-Person Cohort at Enrollment**

| | |
|---|---|
| Age, years | 60 (52-66) |
| Education, years | 14 (12-16) |
| Sex, male | 169 (56.3%) |
| Body mass index, kg/m$^2$ | 29 (26-34) |
| Etiology* | |
| Hepatitis C | 30% |
| Alcohol | 22% |
| NAFLD | 21% |
| Other | 25% |
| Hepatocellular carcinoma | 22 (7.3%) |
| Child class A | 208 (70%) |
| Varices | 229 (76%) |
| Ascites | 122 (41%) |
| Platelet count <80,000 | 111 (37%) |
| Any current alcohol use | 92 (31%) |
| Current alcohol abuse | 22 (7.3%) |
| CCI | 4 (1-4) |
| Laboratory values | |
| MELD-Na | 9 (7-13) |
| Bilirubin (mg/dL) | 1 (0.7-1.6) |
| Creatinine (mg/dL) | 0.9 (0.70-1.04) |
| INR | 1.1 (1.0-1.2) |
| Sodium (meq/L) | 140 (138-141) |
| Albumin (mg/dL) | 4 (3.6-4.3) |
| Markers of frailty | |
| Incompletely independent in ADLs | 27 (9%) |
| Chair stands | 10 (7-13) |
| Hand grip, kg | 31 (22-39) |
| Self-reported falls in past 6 months | 65 (22%) |
| Medication reconciliation (chronic current use) | |
| Diuretics | 120 (40%) |
| Nonselective beta-blockers | 180 (60%) |
| Proton pump inhibitor | 128 (43%) |
| Benzodiazepine | 55 (18%) |
| Gabapentin/pregabalin | 45 (15%) |
| Opiate | 67 (22%) |
| Antidepressant | 54 (18%) |
| Antipsychotic | 21 (7%) |
| Inhibitory control test performance | |
| Lures | 12 (7-22) |
| Targets | 94.3 (84-98) |
| Weighted lures | 14.5 (8.2-37.8) |
| Cannot complete ICT | 39 (13%) |

Categorical values are presented as number and percent. Continuous variables are presented as median (IQR).
*Some patients had both hepatitis C and alcohol-related liver disease.

on ICT-weighted lure values. Overall cognitive performance measured as lures, targets, or weighted-lure values were not different with respect to sex, Child class, benzodiazepine or opiate use, alcohol abuse, or alcohol versus other causes of cirrhosis (Table 1). Of note, 37 (12.3%) patients could not perform the ICT; 22 became frustrated and quit, 10 could not understand instructions, and 5 had adverse reactions (such as dizziness).

## ASSOCIATIONS WITH QUALITY OF LIFE

The median SF-8 score for HRQOL was 70 (interquartile range [IQR], 54-86), with 59 (20%) reporting scores <50. Figure 1 shows the average raw SF-8 score for the entire cohort and subgroups. In Table 2, we show that HRQOL was associated with education, etiology of liver disease (alcohol related), severity

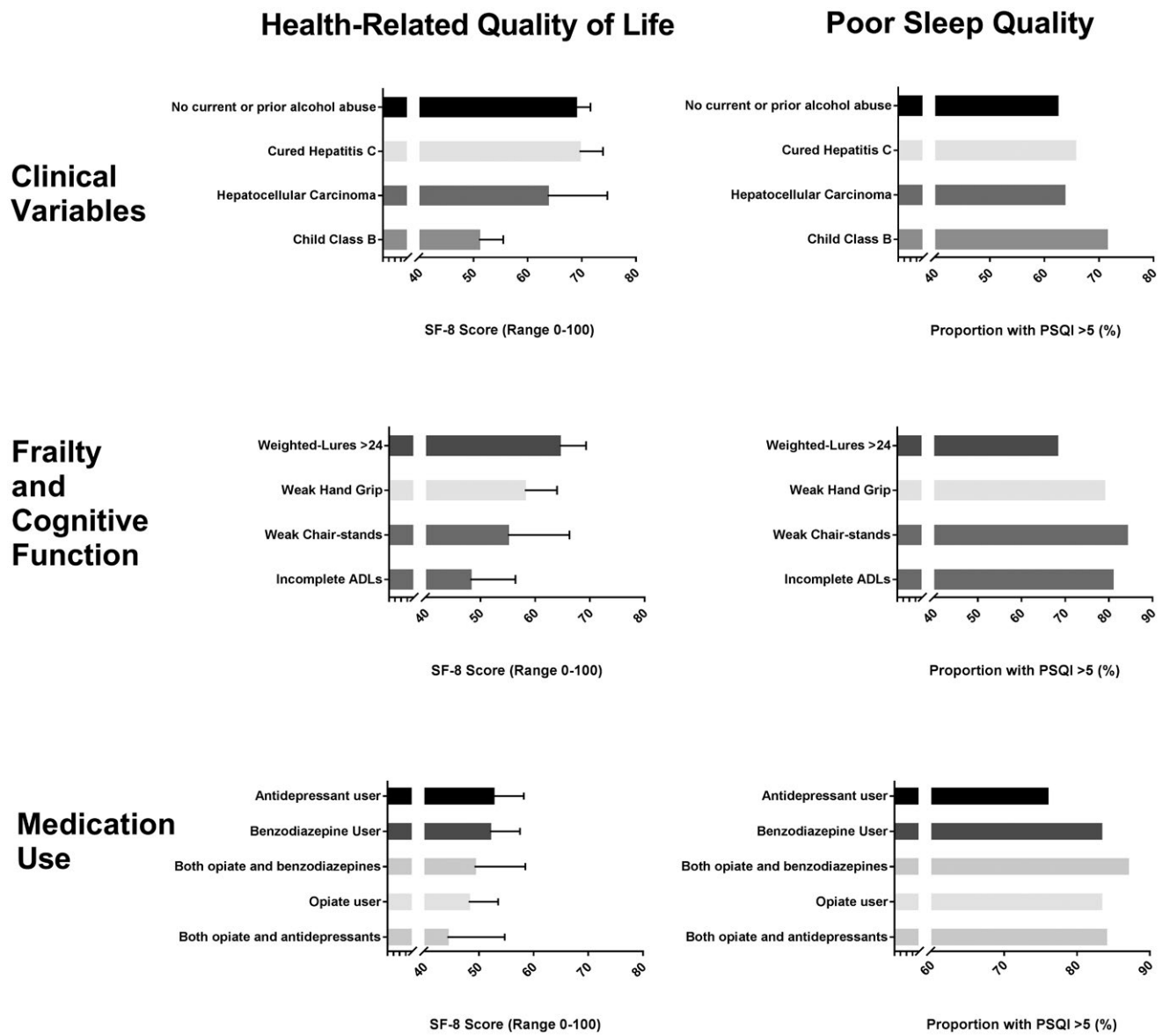


**FIG. 1.** HRQOL and sleep quality in population subgroups. Left side: Each bar displays the median (IQR) SF-8 score for sample subgroups. High SF-8 score indicates better quality of life. Right side: Each bar displays the proportion of patients with Pittsburgh Sleep Quality Indices >5 (indicating poor sleep quality).

**TABLE 2. Uni- and Multivariate Associations With Quality of Life**

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | Effect Estimate (95% CI) | *P* Value | Effect Estimate (95% CI) | *P* Value |
| Age (per year) | 0.16 (–0.05 to 0.36) | 0.13 | | |
| Education (per year) | 1.33 (0.13-2.52) | 0.03 | **1.09 (0.10-2.09)** | **0.03** |
| Male | –0.88 (–3.54 to 1.78) | 0.52 | | |
| Body mass index (per point) | –0.47 (–0.87 to –0.06) | 0.02 | –0.16 (–0.52 to 0.19) | 0.36 |
| CCI (per point) | –0.59 (–1.36 to 0.18) | 0.13 | | |
| Hepatitis C | –1.06 (–7.24 to 5.12) | 0.74 | | |
| ALD | –7.03 (–13.7 to –0.37) | 0.04 | –1.98 (–4.97 to 1.00) | 0.19 |
| NAFLD | –1.98 (–8.90 to 4.93) | 0.57 | | |
| Hepatocellular carcinoma | 0.70 (–4.77 to 6.18) | 0.80 | | |
| Child class B | –3.81 (–6.72 to –0.89) | 0.01 | –0.49 (–3.60 to 2.62) | 0.75 |
| Varices | –0.70 (–3.88 to 2.48) | 0.67 | | |
| Ascites | –1.19 (–3.87 to 1.50) | 0.38 | | |
| Platelet count <80,000 | –2.64 (–5.39 to 0.11) | 0.06 | | |
| Alcohol abuse | –0.72 (–5.73 to 4.28) | 0.78 | | |
| MELD-Na (per point) | –0.66 (–1.02 to –0.19) | 0.008 | –0.40 (–0.90 to 0.09) | 0.11 |
| Bilirubin (per mg/dL) | –2.40 (–4.14 to –0.67) | 0.007 | | |
| Creatinine (per mg/dL) | 0.57 (–2.61 to 3.76) | 0.72 | | |
| INR (per point) | –12.0 (–21.5 to –2.63) | 0.01 | | |
| Sodium (per meq/L) | 0.26 (–0.02 to 0.53) | 0.06 | | |
| Albumin (per mg/dL) | 6.54 (1.87 – 11.2) | 0.006 | 2.20 (–3.03 to 7.43) | 0.41 |
| Falls | –8.16 (–11.4 to –4.95) | <0.0001 | –2.69 (–0.19 to 5.57) | 0.07 |
| Chair stands (per 10 stands) | 11.40 (9.40-18.60) | <0.001 | **9.28 (4.76-13.8)** | **<0.0001** |
| Hand grip (per 10 kg) | 1.90 (–0.10 to 3.90) | 0.06 | | |
| ADL dependence | –9.46 (–14.8 to –4.08) | 0.0006 | **–6.06 (–10.8 to –1.36)** | **0.01** |
| Diuretics | –1.20 (–3.68 to 1.28) | 0.34 | | |
| Nonselective beta-blockers | –0.79 (–3.27 to 1.69) | 0.53 | | |
| Proton pump inhibitor | –3.27 (–5.93 to –0.60) | 0.02 | 1.17 (–1.23 to 3.57) | 0.34 |
| Benzodiazepine | –6.17 (–9.79 to –2.54) | 0.0009 | **–3.50 (–6.58 to –0.42)** | **0.03** |
| Gabapentin | –5.79 (–9.35 to –2.23) | 0.002 | –1.81 (–5.02 to 1.40) | 0.27 |
| Opiate | –10.4 (–13.5 to –7.30) | <0.0001 | **–5.01 (–7.84 to –2.19)** | **0.0006** |
| Tricyclic antidepressant | –4.90 (–8.88 to 0.92) | 0.02 | –1.40 (–5.34 to –2.55) | 0.49 |
| Antidepressant | –6.39 (–9.88 to –2.90) | 0.0004 | –3.01 (–6.47 to 0.46) | 0.09 |
| Antipsychotic | –4.96 (–9.96 to 0.04) | 0.05 | | |
| ICT lures (per lure) | –0.21 (–0.46 to 0.04) | 0.10 | | |
| ICT targets (per target) | 0.11 (–0.09 to 0.31) | 0.26 | | |
| Weighted lures (per point) | –0.14 (–0.26 to –0.02) | 0.04 | **–0.10 (–0.20 to 0.001)** | **0.049** |

Estimates reflect the results of a linear regression and should be interpreted as a positive or a negative effect on quality of life. The multivariable analysis included all variables with $P < 0.05$ in the univariable analysis. We also included age, sex, and Child class given the biological association of these variables with the other candidate covariates. We did not include bilirubin or INR in the multivariable model given collinearity with MELD-Na. Bolded values indicate statistical significance at the 5% level in multivariate analysis.
Abbreviation: ALD, alcoholic liver disease.

of liver disease (Child class B, MELD-Na), use of psychoactive medications (antidepressants, opiates, benzodiazepines, and gabapentin), frailty (ADL performance, chair-stands, and falls) and cognitive function (weighted-lures). When we adjusted these results for one another (with forced inclusion of age, sex, and MELD-Na), the remaining significant variables included education, chair-stands, ADL dependence, benzodiazepine use, opiate use, and weighted-lures. This final model had an $R^2$ of 0.36, suggesting that it explained a substantial (36%) portion of the variance in quality of life in our cohort. For comparison, the

respective univariable $R^2$ associated with MELD-Na, education, chair-stands, ADL dependence, benzodiazepine use, opiate use, and weighted-lures was 0.02, 0.03, 0.15, 0.07, 0.07, 0.03, and 0.04, respectively.

In Supporting Table S1, we performed a logistic regression conditioned on poor HRQOL (SF-8 score <50). In this analysis, only chair-stands (odds ratio [OR] per 10-stands, 0.24; 95% confidence interval [CI; 0.11-0.56]) and weighted-lures (OR per weighted-lure, 1.01 [1.00-1.03]) were significantly associated with poor HRQOL. In a sensitivity analysis excluding ICT performance, chair-stands (OR, 0.34;95% CI [0.17-0.72]) and falls (2.20 [1.06-4.59]) were associated with poor HRQOL.

## QUALITY OF LIFE IN CLINICALLY IMPORTANT SUBGROUPS

In Fig. 1 and Table 3, we demonstrate model estimates in subgroups relevant to clinical practice. Only opiate use was consistently associated with poor HRQOL across subgroups. Chair-stands, a measure of frailty, was associated with HRQOL in all groups save for those with ascites or diuretic use. A history of ascites, when present, was an over-riding determinant of HRQOL. The magnitude of the association between chair-stands and HRQOL was substantially greater for patients with Child A cirrhosis (severity of liver disease was an over-riding determinant of HRQOL in those with Child B cirrhosis). Cognitive function, as measured by weighted-lures, was associated with HRQOL only in patients with cured hepatitis C, no past alcohol abuse, and those not on opiates or benzodiazepines.

## ASSOCIATIONS WITH POOR SLEEP

Our patients reported a median PSQI score of 7 (IQR, 4-11), 187 (63%) of whom had poor sleep (PSQI >5). Although poor sleep was highly prevalent, we show that specific subgroups had greater burdens of poor sleep (Fig. 1). This included, for example, patients with Child B cirrhosis (71.4%), those with weak chair-stand performance (84.1%), and users of opiates and benzodiazepines (87.0%). We excluded benzodiazepines from regression analyses given that they are often used explicitly for poor sleep. Many factors that were strongly associated in

**TABLE 3. HRQOL in Subgroups**

| Covariate | Child A (n = 208) | Ascites or Diuretics (n = 143) | Cured Hepatitis C (n = 91) | No Current or Past Alcohol Abuse (n = 232) | No Current Opiate or Benzodiazepine Use (n = 202) |
|---|---|---|---|---|---|
| Chair stands (per 10 stands) | 13.1 (7.27-18.90) | | 7.92 (0.26 to 15.60) | 7.99 (3.24 to 12.73) | 9.52 (4.40 to 14.63) |
| Opiate use (yes vs. no) | −4.90 (-8.29 to −1.50) | −6.62 (−10.7 to −2.53 | −5.50 (−10.9 to −0.13) | −5.17 (−8.36 to −1.98) | |
| MELD-Na (per point) | | −0.77 (−1.36 to −0.18) | | | −0.68 (−1.13 to −0.22) |
| Antidepressants (yes vs. no) | | −4.24 (−8.31 to −0.18) | | | |
| Weighted lures (per point) | | | −0.16 (−0.32 to −0.006) | −0.13 (−0.23 to −0.02) | −0.17 (−0.28 to −0.06) |
| Incomplete ADLs (yes vs. no) | | | | −4.81 (−9.24 to −0.38) | −5.84 (−10.6 to −1.11) |
| Benzodiazepines (yes vs. no) | | | | −4.14 (−7.57 to −0.71) | |

HRQOL is scored on a scale from 0 to 100. Results of the multivariable model from Table 2 for subgroups. Only the significant results are depicted for each subgroup. Each estimate is the result of a linear regression with a 95% CI, indicating a positive or a negative impact on HRQOL score. Gray shading indicates a nonsignificant result ($P \geq 0.05$); black shading indicates that the variables were excluded from the model.

a univariate analysis, including liver disease severity and frailty, were not significant in multivariable analysis. In Supporting Table S2, we detail the results of a multivariable logistic regression that found that only two factors were significantly associated with poor sleep: opiate use (OR, 2.85; 95%CI [1.11-7.29] and weighted-lures (1.03 [1.00-1.05]). In a sensitivity analysis excluding ICT performance, opiates (2.23 [1.04-4.78]), Child B (2.11 [1.16-3.82]), and chair-stands (per 10-stands; OR, 0.58 [0.34-0.98]) were associated with poor sleep.

# Discussion

The lived experience of cirrhosis can be very challenging for many patients, marked by debilitating symptoms and poor HRQOL.[3] Poor PROs have been traditionally associated with cirrhosis complications such as ascites and overt HE.[4-8] However, this prospective study of 300 generally clinically stable outpatients with cirrhosis, half of whom had no history of decompensation and none had a history of overt HE, highlight other, potentially modifiable targets for suboptimal PROs. Specifically, we found that markers of frailty, psychoactive medications, and cognitive function were associated with HRQOL and sleep quality.

These data come at an important time in the history of chronic liver disease. The prevalence of cirrhosis is rising because of the increasing prevalence of nonalcoholic fatty liver disease (NAFLD) and alcohol-related liver disease.[30,31] At the same time, as we approach the eradication of hepatitis C, we expect to arrest the natural history of cirrhosis for many patients, extending lives substantially. Thus, more patients are living with cirrhosis and will be living longer. Awareness of, and efforts to improve, PROs are needed.

## A CONCEPTUAL MODEL OF QUALITY OF LIFE IN CIRRHOSIS WITH PORTAL HYPERTENSION

Adjusting for severity of liver disease, age, and education, we found associations with HRQOL and poor sleep quality that extend current knowledge in important ways. First, several studies have shown that frailty is common and associated or correlates with poor quality of life in patients with end-stage liver disease.[32,33] Our data showed that this is also true in a population with earlier-stage cirrhosis, highlighting the importance of recognizing and managing frailty across the stages of cirrhosis. The relationship between frailty and poor HRQOL is likely complex; although muscle weakness may interfere with activities, it may also reflect qualitatively more-severe comorbidities and cognitive dysfunction. The association between chair-stands and poor sleep underscores that frailty reflects a global disorder that impacts PROs beyond physical function.

Second, we found that impaired cognitive function, as measured by ICT performance, is associated with poor HRQOL. The ICT has been used for diagnosis of covert HE.[34] Nabi et al. previously exploited the relationship between covert HE and poor HRQOL and showed that a four-question modification of the Sickness Impact Profile HRQOL tool, can be used to indicate risk for, if not diagnose, covert HE.[35] Our data showed that ICT performance can also identify patients with poor HRQOL. However, we found that impaired cognitive function had a greater impact on HRQOL in patients with neither alcohol abuse histories nor psychoactive medication use. As we have reviewed elsewhere,[36] the ICT, like other tests of covert HE, has not been validated in patients with alcohol abuse or those on psychoactive medications. For this important subset of patients, alcohol, opiate, or benzodiazepine use may diminish their ability to carry out these tests and confound the results. Indeed, we found that an important subgroup of patients could not perform the ICT. In order to assess associations with ICT scores, this subgroup must be excluded, thereby masking associations between poor sleep quality, psychoactive medications, and frailty.

Third, we showed that chronic opiate and benzodiazepine use is common in patients with cirrhosis and negatively impact PROs. These data in patients with clinically stable cirrhosis extend results from Ghabril et al., who demonstrated an impact of opiates on HRQOL and sleep quality in patients with decompensated cirrhosis.[8] We acknowledge that poor HRQOL in these patients may be driven by the indications for opiate or benzodiazepine use and not necessarily a direct effect of these medications in patients with cirrhosis.[37] However, these medications are well recognized to have adverse effects in patients with cirrhosis and can often be substituted for safer therapies without worsening symptoms and other PROs.[10,13]

## TARGETS FOR FUTURE ACTION

Our cross-sectional data highlight three paths for future studies aimed at improving PROs through multimodal interventions that reduce the adverse effects of polypharmacy, address cognitive dysfunction, and improve physicality/frailty. First, though these data cannot disentangle the effect of psychoactive medications from confounding by indication, their association with HRQOL justifies a prospective trial of deprescribing. Psychoactive medications, such as opiates or benzodiazepines, can often be discontinued or substituted with nonpharmacological treatments (e.g., talk-therapy for anxiety, sleep-hygiene training for insomnia, and physical therapy for back pain), avoiding side effects without therapeutic failure, and may even improve quality of life.[10,38] In addition to the potential value in improving HRQOL, there is a physiological rationale for deprescribing psychoactive medications in patients with cirrhosis. Benzodiazepines sedate while potentiating inhibitory (GABAergic) tone; opiates sedate while decreasing intestinal motility, potentially increasing the absorption of ammonia and bacterial translocation.[9] These mechanisms are both implicated in HE. In light of the recent opioid epidemic, many studies been conducted to evaluate the efficacy of alternative, less-addictive approaches to pain control in nononcology settings showing similar effectiveness. Although worsened HRQOL is a theoretical risk after opiate discontinuation, the available data actually support withdrawal.[10,13] These data support a position of clinical equipoise and justify similar clinical trials in patients with cirrhosis.

Second, by identifying patients with suboptimal performance on cognitive testing, we may initiate therapeutic trials—including lactulose—that could have the potential to improve quality of life.[7] Third, interventions for patients with frailty, such as improved nutritional support and physical therapy, may result in improvements in quality of life.[39-41] These interventions have been shown to be effective in improving HRQOL in patients with advanced cirrhosis on the liver transplant waiting list, but have not been studied in patients with Child A cirrhosis, a more clinically stable population in whom such interventions are easier to implement.

## CONTEXTUAL FACTORS

Our data must be interpreted in the context of the study design. First, this cross-sectional analysis cannot establish causation. Our data are at risk for confounding by indication (pain and anxiety for which psychoactive medications are prescribed are also linked with poor HRQOL). Second, our cohort best reflects the characteristics of patients seen at a tertiary referral center and may not generalize to other patients with cirrhosis.

Deficits in quality of life are present even in patients with predominantly Child A cirrhosis. These findings underscore the need for a holistic assessment of our patients and highlight opportunities to improve PROs in patients with cirrhosis. Our data support the role for a multifactorial intervention aimed at reducing polypharmacy, improved physical function, and testing-and-treating of cognitive dysfunction.

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# Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.30336/suppinfo.