


Sleep Disturbance Is Associated With the Presence of Portosystemic Collaterals in Patients With Compensated Cirrhosis

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Disturbed sleep is common among patients with cirrhosis. The extent to which this is associated with the different stages of compensated cirrhosis is unknown. This study examines whether the presence of portosystemic collaterals, an indicator of clinically significant portal hypertension, is associated with sleep disturbance in compensated cirrhosis. We conducted a cross-sectional study among patients with compensated cirrhosis, comparing sleep characteristics, sleep quality, and excessive daytime sleepiness between 21 patients without and 21 patients with portosystemic collaterals. Patients were assessed with wrist actigraphy, Pittsburgh Sleep Quality Index, and the Epworth Sleepiness Scale. Collateral presence was determined by imaging and esophagogastroduodenoscopy. Differences in sleep characteristics were analyzed using *t* tests and computed effect sizes. Multivariable linear regression analysis was used to evaluate the association between collaterals and sleep disturbance while controlling for possible confounders. The group of patients with collaterals had greater beta-blocker and tobacco use, lower albumin, and higher international normalized ratio compared to the group without collaterals. Patients with collaterals had more sleep fragmentation (Cohen's *d* = -0.86), lower sleep efficiency (Cohen's *d* = 0.59), and lower total sleep time (Cohen's *d* = 0.75) than patients without collaterals. The presence of collaterals was independently associated with greater sleep fragmentation (*P* = 0.046) and greater daytime sleepiness (*P* = 0.030). **Conclusion:** Patients with compensated cirrhosis complicated by portosystemic collaterals experienced more sleep disturbance than those without collaterals. (*Hepatology Communications* 2021;5:491-501).

Sleep disturbance is common among patients with cirrhosis, occurring in nearly half the population.⁽¹⁾ Patients with cirrhosis take longer to fall asleep, have more fragmented sleep, experience prolonged sleep latency, and take more daytime naps than healthy individuals.⁽¹⁾ In fact, sleep disturbance has been one of the symptoms that have been used to define covert hepatic encephalopathy (HE; previously known as minimal HE).⁽²⁾ Despite its prevalence,

much remains unknown regarding the causes and prognostic significance of sleep disturbance (or covert HE) in patients with cirrhosis, mostly because these alterations have been investigated in mixed cohorts of patients with both compensated and decompensated cirrhosis, even including patients with a history of overt HE.^(1,3-6)

We now know that the natural history of cirrhosis is characterized by a progression from an early

Abbreviations: BMI, body mass index; CSPH, clinically significant portal hypertension; Epworth, Epworth Sleepiness Scale; HE, hepatic encephalopathy; MOCA, Montreal cognitive assessment; PSQI, Pittsburgh Sleep Quality Index; SE, sleep efficiency; SF, sleep fragmentation; SOL, sleep onset latency; TMT-A/B, Trail Making Test A/B; TST, total sleep time; WASO, wake after sleep onset.

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compensated stage to an advanced decompensated stage. Development of variceal hemorrhage, ascites, jaundice, or overt HE defines decompensation, and once this develops median survival decreases from >10 years to 2 years.^(7,8) The main pathophysiological mechanism in the compensated stage is portal hypertension, while systemic vasodilatation and liver insufficiency are main pathogenic mechanisms in the decompensated stage.

Compensated cirrhosis is stratified into two sub-stages based on the absence or presence of clinically significant portal hypertension (CSPH), with the latter being defined as a portal pressure gradient ≥ 10 mm Hg and being the main predictor of decompensation. The term “clinically significant” is not only related to a higher likelihood of developing decompensation⁽⁹⁾ but also patients with CSPH are more likely to have thick fibrous septa on liver biopsy and a hyperdynamic circulatory state (absent in those without CSPH) amenable to treatment with nonselective beta-blockers.⁽⁷⁾

Per the Baveno Consensus Conference, a noninvasive surrogate of CSPH is the presence of portosystemic collaterals, either gastroesophageal varices observed endoscopically or collaterals observed on cross-sectional imaging.⁽⁸⁾ Patients with collaterals have more altered systemic hemodynamics (more vasodilatation, higher cardiac output), worse liver function, more inflammation, and a poorer prognosis than patients with cirrhosis without portosystemic collaterals.⁽⁹⁻¹¹⁾

It is plausible that sleep disturbance in cirrhosis is associated with the presence of portosystemic collaterals. This is based on observed associations between portosystemic collaterals and biologic mechanisms that can produce sleep disturbance, such as circadian rhythm alterations^(12,13) and greater systemic

inflammation.⁽¹⁴⁻¹⁷⁾ The relationship between CSPH/collaterals and sleep disturbances has never been evaluated in a well-characterized cohort of patients with compensated cirrhosis. Establishing whether such an association exists has important implications for understanding the prognostic significance and mechanisms of sleep disturbance and even covert HE among patients with cirrhosis.

The purpose of this proof-of-concept study was to compare sleep parameters between patients with compensated cirrhosis with and without portosystemic collaterals (as a surrogate of CSPH) with the hypothesis that those with portosystemic collaterals would have poorer sleep quality, more sleep fragmentation (SF), and more daytime sleepiness.

Participants and Methods

STUDY DESIGN

We conducted a prospective cross-sectional proof-of-concept study at the VA-Connecticut Healthcare System and Yale University between October 2013 and January 2015. Institutional review board approval was obtained. All participants provided written informed consent.

We included adults who had compensated cirrhosis and had completed esophagogastroduodenoscopy for varices and cross-sectional imaging for hepatocellular cancer screening within 1 year of data collection. The two comparison groups were patients without and with portosystemic collaterals.

The presence of portosystemic collaterals was determined based on two parameters: presence of varices by endoscopy or presence of portosystemic collaterals on imaging. Any communication between

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the portal and the systemic venous system visualized on cross-sectional imaging (computed tomography or magnetic resonance imaging) was classified as portosystemic collaterals.

In patients without portosystemic collaterals, cirrhosis was confirmed by the following standard criteria: liver biopsy with stage 4 fibrosis, hepatic venous pressure gradient greater or equal to 6 mm Hg, and/or a combination of nodular liver, splenomegaly, and platelet count $\leq 150,000/\mu\text{L}$. In patients with portosystemic collaterals, cirrhosis was confirmed by compatible clinical, imaging, and/or histologic features.

Exclusion criteria included decompensated cirrhosis (ascites, history or presence of variceal hemorrhage, history or presence of overt HE, or jaundice), hepatocellular carcinoma, cholestatic liver disease, portal vein thrombosis, prior or current HE treatment, ongoing interferon treatment, human immunodeficiency virus infection, body mass index (BMI) $\geq 40 \text{ kg/m}^2$, heavy alcohol or recreational drug use within 6 months of enrollment, daily sleep or benzodiazepine medication use, known primary neurologic or sleep disorder, head trauma, uncontrolled psychiatric disease, and presence of a medical comorbidity that would interfere with data collection or limit life expectancy to less than 2 years.

VARIABLES AND MEASURES

Objective Sleep Characteristics

Objective sleep characteristics were assessed with 7 days of continuous wrist actigraphy (Respironics Minimitter Actiwatch AW-64). The 7-day period was chosen in order to sample weekday and weekend patterns. Actigraphs estimate sleep timing based on wrist motor activity monitored by a small accelerometer. Actigraphy was used to compute total sleep time (TST), sleep efficiency (SE), nighttime awakenings, wake after sleep onset (WASO), and sleep percentage, and all variables were valid compared with polysomnography.⁽¹⁸⁻²¹⁾

Data were collected in 30-second epochs, and participants were instructed to wear the actigraph on their nondominant wrist at all times except for bathing, to depress the event marker at lights on and lights off, and refrain from alcohol, recreational drugs, benzodiazepines, opiates, and any sleep medication use for the duration of actigraphy. Participants recorded times of

actigraph removal and replacement and time of lights off and lights on in the daily sleep diaries to assist with actigraphy scoring.

Event marker and sleep diary recordings were used to identify time of lights off and time of lights on for determination of the sleep period. The following sleep characteristics were computed:

1. Total time in bed was defined as minutes from lights off to getting out of bed in the morning.
2. Sleep onset latency (SOL) was defined as minutes from lights off to sleep onset, confirmed by event recordings and activity counts. SOL >30 minutes was considered abnormal.⁽²²⁾
3. WASO was defined as minutes spent awake after sleep onset.
4. TST was defined as time spent asleep at night. TST <6.5 hours was considered abnormal.⁽²²⁾
5. SE was defined as the percentage of time in bed spent as actual sleep time. A higher value indicated better overall sleep quality. SE $<85\%$ was considered abnormal.⁽²²⁾
6. SF was defined as an index of restlessness derived as a ratio of the sum of percent mobile and percent immobile bouts less than 1-minute duration to the number of immobile bouts. A higher value indicated more frequent nighttime arousals and less sleep continuity.

Self- Reported Sleep Quality and Daytime Sleepiness

The Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (Epworth) were used to capture self-reported sleep quality and daytime sleepiness, respectively. The PSQI is a reliable instrument that assesses sleep quality over 1 month. An overall score ranges from 0 to 21 points. A higher score signifies a worse sleep quality; a score ≥ 5 indicates poor overall sleep quality.⁽²³⁾ We derived self-reported TST, SOL, and SE from the habitual bedtimes and sleep times reported on the PSQI.

The Epworth is a validated eight-item questionnaire that assesses daytime sleepiness, meaning how likely an individual is to fall asleep during the daytime while engaged in daily activities. Scores range from 0 to 24 points. A higher score signifies a greater sleepiness; a score ≥ 10 indicates significant daytime sleepiness.⁽²⁴⁾

Quality of Life

The SF-36 was used to assess health-related quality of life. The SF-36 consists of 36 items that are employed to calculate physical and mental component scores. Scores range from 0 to 100 points, with higher scores corresponding to a better quality of life.

Demographic and Clinical Data

Medical, psychiatric, medication, and social history were determined from interviews; cirrhosis etiology from chart review; and BMI from physical examination. A brief neurocognitive evaluation was performed using the Montreal Cognitive Assessment (MOCA) and Trail Making Test A (TMT-A) and B (TMT-B). Ammonia, a gut neurotoxin associated with HE, was measured using venous samples collected as part of the study procedures.

Because there is not one universally agreed composite measure for subclinical HE,^(25,26) the MOCA, TMT-A, and TMT-B were used to identify subclinical neurocognitive impairments indicative of possible subclinical HE. The MOCA is a widely used and accurate clinical tool for identification of mild cognitive impairment.⁽²⁷⁾ A score ≤ 26 (out of a total of 30), corrected for education level, is considered impaired.⁽²⁷⁾ TMT-A and TMT-B are pencil and paper tests that require the subject to draw lines connecting numbers (TMT-A) or alternating numbers and letters (TMT-B) in ascending order. Both have been used in previous studies for evaluation of cognitive impairment among patients with cirrhosis and cumulatively measure attention, visuospatial perception, psychometric speed, and executive function.^(28,29) The raw score for each test (i.e., the time in seconds required to complete each) was converted to a scaled value, and *t* scores were then adjusted for age, sex, ethnicity, and education using the Heaton normal, as is standard and is well validated.⁽³⁰⁾

Data Analysis

Actigraphy data were downloaded and scored using Actiware version 6 software (Respironics Minimitter Inc.). Data analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC). Descriptive statistics were used to describe the demographic, clinical, and outcome variables between the

groups, characterized by the presence or absence of collaterals. Demographic, clinical, and neurocognitive values were skewed; therefore, median values were reported, and the variables were compared using nonparametric testing (Wilcoxon Rank Sum/Mann-Whitney U). Actigraph-derived sleep characteristics, PSQI overall score, and Epworth were normally distributed; therefore, means and SDs were reported, and the variables were compared using Student *t* tests. Categorical variables were compared using chi-squared tests.

We did not perform an *a priori* power calculation because of the exploratory nature of the study. We computed the size of the group differences in the objective sleep characteristic and self-reported sleep quality and daytime measures using standard effect size calculations because of the small sample and exploratory nature of the study and our interest in using these data to support a larger more fully powered study. Cohen's definitions for effects sizes were used, where an effect size absolute value of 0.2 was considered small, an effect size of 0.5 medium, and an effect size of 0.8 large.⁽³¹⁾

Multivariable linear regression was performed to explore the independent association between portosystemic collateral presence and sleep disturbance. Three separate regression models were constructed using three different dependent variables: actigraph-measured SE, actigraph-measured SF, and the Epworth. We chose SE and SF because they are objective composite measures of overall sleep quality and sleep continuity, respectively. We chose Epworth because it is a validated daytime sleepiness measure. Because of the small sample size, we could include only a limited number of covariates in the multivariable linear regression and ultimately controlled for tobacco⁽³²⁾ and beta-blockers⁽³³⁾ because they are known causes of sleep disturbance and were significantly different in frequency between groups.

Last, we performed an exploratory univariate analysis to evaluate the association between each sleep measure and quality of life. The median for each sleep measure was used to classify patients into the two groups "high" versus "low" sleep disturbance. The nonparametric Wilcoxon rank sum test was used to compare median SF-36 physical and mental component scores between groups.

Results

Forty-two patients with compensated cirrhosis (21 without and 21 with portosystemic collaterals) enrolled and completed all study procedures. There were no significant differences in age or median Model for End-Stage Liver Disease score between groups (Table 1). Compared to the group without collaterals, the collateral group had more men, lower albumin, higher international normalized ratio levels, and lower platelet counts. In addition, the collateral group had more tobacco and more beta-blocker use (as expected because these drugs are used to

prevent variceal bleeding). There were no significant between-group differences in psychiatric disease, alcohol, sleep medication, benzodiazepine, methadone/opiate use, neurocognitive testing, or ammonia levels.

ACTIGRAPH-MEASURED SLEEP CHARACTERISTICS

Actigraph-measured sleep characteristics for the overall sample and by comparison group are presented in Table 2. SF was significantly higher among patients with collaterals than patients without collaterals, with

TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Variable	Overall (n = 42)	Portosystemic Collaterals Absent (n = 21)	Portosystemic Collaterals Present (n = 21)
Age (years)	61 (44-68)	61 (44-68)	61 (44-67)
Male*	34 (81%)	14 (67%)	20 (95%)
MELD score	8 (6-14)	8 (6-13)	9 (6-14)
Etiology of cirrhosis			
HCV	21 (50%)	12 (57%)	9 (43%)
Alcohol	6 (14%)	1 (5%)	5 (24%)
HCV+alcohol	10 (24%)	5 (24%)	5 (24%)
Autoimmune	5 (12%)	3 (14%)	2 (10%)
Active controlled psychiatric disease	19 (45%)	11 (52%)	8 (38%)
Substance use disorder in remission	32 (76%)	15 (71%)	17 (81%)
Social alcohol use	3 (7%)	1 (5%)	2 (10%)
Tobacco use*	14 (33%)	4 (19%)	10 (48%)
Current beta-blocker use*	17 (40%)	4 (19%)	13 (62%)
Occasional sleep medication use	7 (17%)	4 (19%)	3 (14%)
Occasional benzodiazepine use	3 (7%)	2 (10%)	1 (5%)
Methadone use	4 (10%)	3 (14%)	1 (5%)
Opiate pain medication use	1 (2%)	0 (0%)	1 (5%)
BMI (kg/m ²)	29.4 (18.8-38.3)	29.6 (18.8-38.3)	27.9 (22.7-36.3)
Albumin*	3.70 (2.80-4.40)	3.70 (3.10-4.40)	3.50 (2.80-4.40)
AST (U/L)*	38 (12-161)	30 (12-161)	53 (20-149)
ALT (U/L)	31 (8-186)	29 (8-186)	42 (12-139)
Total bilirubin (mg/dL)	0.90 (0.34-2.79)	0.73 (0.37-2.21)	0.98 (0.34-2.79)
INR*	1.10 (1.00-1.60)	1.10 (1.00-1.40)	1.10 (1.00-1.60)
Platelets × 10 ³ /L*	120 (31-419)	148 (31-419)	96 (35-190)
Ammonia (µg/dL)	24 (9-48)	24 (9-40)	24 (9-48)
MOCA education-adjusted score	25 (20-30)	26 (20-30)	25 (20-30)
TMT-A (f score)	45.5 (25.0-76.0)	44.0 (25.0-76.0)	48.0 (33.0-69.0)
TMT-B (f score)	46.5 (12.0-73.0)	46.0 (12.0-72.0)	48.0 (32.0-73.0)

Data presented as median (range) or number (percentage).

**P* < 0.05 for difference between groups; Wilcoxon Rank Sum/Mann-Whitney U test or chi-squared analysis used where appropriate.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

TABLE 2. SLEEP CHARACTERISTICS MEASURED BY WRIST ACTIGRAPHY

Characteristic	Overall (n = 42)	Portosystemic Collaterals Absent (n = 21)	Portosystemic Collaterals Present (n = 21)	Effect Size*
Time in bed, minutes/night	421.77 (94.93)	444.27 (101.8)	399.27 (83.95)	0.48
SOL, minutes/night	28.86 (33.95)	24.2 (12.76)	33.52 (46.41)	-0.27
WASO, minutes/night	120.63 (66.38)	108.81 (73.38)	132.44 (57.94)	-0.36
TST, minutes/night	298.51 (104.10)	335.46 (113.99)	261.56 (79.71)	0.75
SE, % [†]	64.13 (16.72)	68.88 (15.3)	59.38 (17.07)	0.59
SF, index [‡]	25.68 (8.80)	22.17 (6.24)	29.2 (9.69)	-0.86

All values expressed as mean (SD).

*Effect size for difference between groups expressed as Cohen's *d*, where 0.2 is small, 0.5 is medium, and 0.8 is large.

[†]*P* < 0.10 for difference between groups.

[‡]*P* < 0.05 for difference between groups.

a large effect size observed in the magnitude of difference (Cohen's *d* = -0.863; *P* = 0.009).

Moderate effect sizes were observed for the differences in TST and SE between groups. Although the differences did not reach statistical significance, the effect size magnitudes suggested a trend toward lower TST and lower SE in patients with collaterals compared to those without (Cohen's *d* = 0.751 and Cohen's *d* = 0.586, respectively) (Fig. 1).

The effect sizes for between-group differences in time in bed, WASO, and SOL were small to moderate and not statistically significant. The effect sizes for the differences suggested a possible trend toward longer time in bed (Cohen's *d* = 0.48), more WASO (Cohen's *d* = 0.36), and longer SOL (Cohen's *d* = 0.27) among patients with portosystemic collaterals than those without collaterals. Post-hoc power calculations indicated that 21 patients per group provided 80% power to detect an effect size of 0.885 with 5% type 1 error.

SELF-REPORTED SLEEP QUALITY AND DAYTIME SLEEPINESS

Poor self-reported sleep quality and excessive daytime sleepiness were highly prevalent across the entire study population; 84% had a PSQI >5 and 27% had an Epworth >10 (Table 3), indicating poor sleep quality and excessive daytime sleepiness, respectively. Twice as many patients with collaterals had excessive daytime sleepiness (42%) than patients without collaterals (22%). Mean Epworth was higher in patients with collaterals compared to those without collaterals, with

a moderate effect size (Cohen's *d* = -0.43), although the difference was not statistically significant. PSQI total scores and measures of self-reported sleep time, SOL, and SE were not significantly different between groups.

ASSOCIATION BETWEEN PORTOSYSTEMIC COLLATERALS AND SLEEP DISTURBANCE

As detailed in the methods section, multivariable linear regression was employed to explore the independent association between portosystemic collaterals and three different measures of sleep and sleepiness (Table 4). The presence of portosystemic collaterals was associated with a 5.791-unit increase in actigraph-measured SF compared to those without collaterals after adjusting for beta-blocker and tobacco use (*P* = 0.046). The presence of collaterals was significantly associated with a 4.199-unit increase in the Epworth compared to those without collaterals after adjusting for beta-blocker and tobacco use (*P* = 0.03). The presence of portosystemic collaterals was not significantly associated with actigraph-measured SE.

SLEEP DISTURBANCE AND QUALITY OF LIFE

As described in the methods section, the median for each sleep measure was used to classify patients into high versus low sleep disturbance groups. Median SF-36 physical and mental composite scores were compared between these two groups.

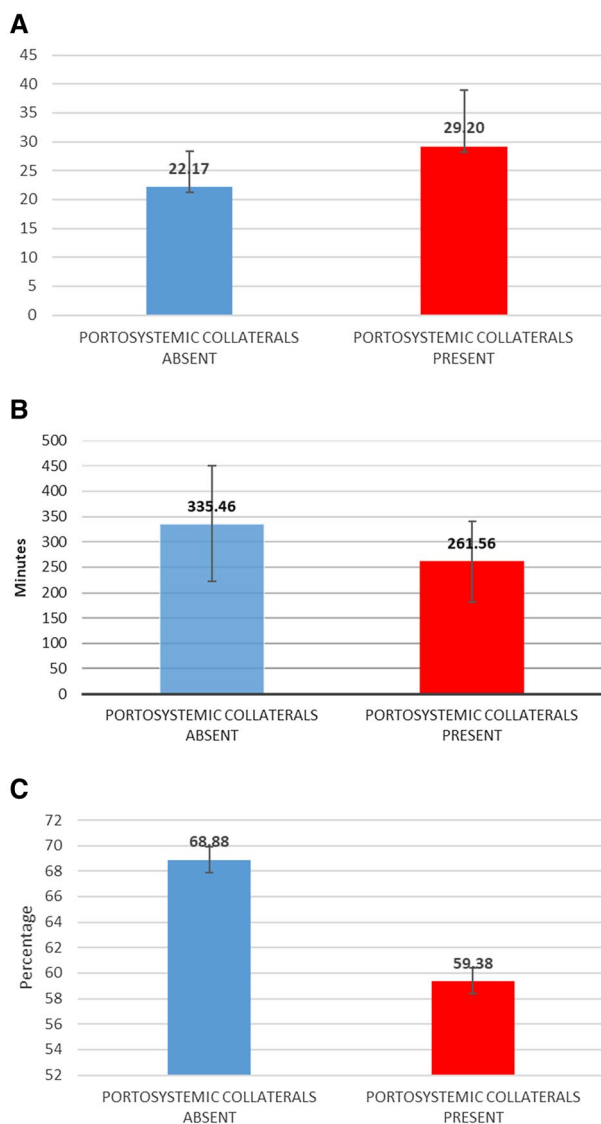


FIG. 1. Sleep characteristics measured by sleep actigraphy. (A) sleep fragmentation (SF), (B) total sleep time, and (C) sleep efficiency (SE) among patients with ($n = 20$) and without ($n = 20$) portosystemic collaterals. Graphs show the average (bars) and SDs (vertical lines) for each measure. SF (a measure of nighttime arousal and sleep continuity), average sleep time, and SE (the percentage of time in bed spent actually sleeping) were all more altered in patients with collaterals.

Using the PSQI, patients with high sleep disturbance had worse physical (9.4; range, 26.6–55.9; vs. 46.6; range, 19.7–60.7; $P = 0.07$) and mental (36.8; range, 18.4–60.4; vs. 49.8; range, 19.9–62.7; $P = 0.02$) composite scores than those with low sleep disturbance. Using the Epworth score, patients with high daytime sleepiness had a worse mental composite score (36.8; range, 18.4–60.4; vs. 49.8; range, 19.9–62.7;

$P = 0.02$) than those with low levels of daytime sleepiness. No significant associations were detected among any other sleep measures and quality of life.

Discussion

To our knowledge, this is the first study that compares objective and self-reported sleep characteristics in a well-characterized cohort of compensated cirrhosis, comparing its two substages based on presence or absence of portosystemic collaterals. We found that sleep continuity (measured by actigraphy computed SF) and daytime sleepiness (measured by Epworth) were worse among patients with portosystemic collaterals (indicative of advanced stage of compensated cirrhosis) compared with those without portosystemic collaterals (early compensated cirrhosis). These findings persisted when controlling for tobacco and beta-blocker medication use.

Moderate to large effect size differences were also detected in total sleep time, time in bed, and SE between the two groups. Although not statistically significant, the differences in these sleep characteristics are worth highlighting because they are dramatic and clinically meaningful. For example, average sleep duration in patients with portosystemic collaterals was over 1 hour shorter (4.4 hours/night) than those without collaterals (5.5 hours/night). Overall sleep quality, measured by actigraph-SE, was much worse among patients with portosystemic collaterals (59% per night) than without collaterals (69% per night). Finally, it is notable that excessive daytime sleepiness was nearly twice as common among patients with collaterals (32%) than patients without collaterals (22%), a finding that has important implications for daytime function. In summary, the later stage of compensated cirrhosis (i.e., characterized by the presence of portosystemic collaterals indicative of CSPH) is associated with greater nighttime arousals and daytime sleepiness.

It is notable that poor sleep quality and excessive daytime sleepiness were highly prevalent across the entire study population. For example, average actigraph-measured SE was 64%, which is much lower than typical normal values (>85%). Actigraph-measured sleep was characterized by delayed sleep onset and highly fragmented nighttime sleep with frequent awakenings, similar to that observed in previous studies among patients with cirrhosis.^(1,3,5,34)

TABLE 3. SELF-REPORT MEASURES OF SLEEP QUALITY AND DAYTIME SLEEPINESS

Measure	Overall (n = 42)	Portosystemic Collaterals Absent (n = 21)	Portosystemic Collaterals Present (n = 21)	Effect Size*
PSQI total score (mean, SD)	9.50 (4.33)	9.68 (4.46)	9.32 (4.31)	0.082
PSQI total score >5 (n,%)	32 (84%)	16 (84%)	16 (84%)	-
PSQI-TST, minutes/night (mean, SD)	6.44 (2.82)	6.37 (1.88)	6.50 (3.51)	-0.045
PSQI-SOL, minutes/night (mean, SD)	33.13 (30.31)	37.37 (33.27)	29.29 (27.63)	0.266
PSQI-SE, % (mean, SD)	77% (18%-83%)	80% (15%-85%)	75% (21%-83%)	0.273
Epworth total score (mean, SD)	7.81 (5)	6.72 (5.1)	8.84 (4.82)	-0.43
Epworth total score >10 (n, %)	10 (27%)	4 (22%)	6 (32%)	—

Hyphen indicates that effect size was not calculated.

*Effect size for difference between groups expressed as Cohen's *d*, where 0.2 is small, 0.5 is medium, and 0.8 is large.

TABLE 4. ASSOCIATION BETWEEN PORTOSYSTEMIC COLLATERALS AND SLEEP DISTURBANCE. (ADJUSTED MULTIVARIATE LINEAR REGRESSION)

Sleep Characteristic		Estimate	Standard Error	P Value
SF (actigraph) Portosystemic collaterals	Absent	Referent		
	Present	5.791	2.804	0.046
Beta-blocker use	Absent	Referent		
	Present	3.118	2.843	0.280
Tobacco use	Absent	Referent		
	Present	-1.465	2.874	0.613
SE (actigraph) Portosystemic collaterals	Absent	Referent		
	Present	-5.826	5.663	0.310
Beta-blocker use	Absent	Referent		
	Present	-10.298	5.550	0.071
Tobacco use	Absent	Referent		
	Present	-2.583	5.455	0.639
Daytime sleepiness (Epworth score) Portosystemic collaterals	Absent	Referent		
	Present	4.199	1.848	0.0301
Beta-blocker use	Absent	Referent		
	Present	-3.642	1.841	0.057
Tobacco use	Absent	Referent		
	Present	0.586	1.841	0.752

All models are adjusted for tobacco and beta-blocker use.

Also, our sample had worse self-reported sleep quality (as measured by the PSQI) and more daytime sleepiness (as measured by the Epworth) than previous

studies in cirrhosis that included mixed study populations consisting of both compensated and decompensated cirrhosis.^(1,3,35) This may be a reflection

of different sleep measures that were used in previous studies and/or inclusion of study subjects who were U.S. military veterans, among whom there is a high background prevalence of disturbed sleep and depression that can manifest in abnormal PSQI and Epworth scores.^(36,37)

Sleep disturbances have been considered manifestations of covert HE and consequent to the effect of shunted gut toxins, mostly ammonia.^(38,39) However, recent studies have questioned this view, finding that nighttime sleep disturbances may occur independent of the neurocognitive impairments characteristic of overt HE. The main strength of our proof-of-concept study, unlike other similar studies, was that we only included patients with compensated cirrhosis (i.e., without any history/presence of variceal hemorrhage, overt HE, or ascites) and used the presence of portosystemic collaterals as a stratifying characteristic. Patients with collaterals (and CSPH) not only have more shunting (from portal/intestinal-derived blood and the systemic circulation) but also have more histologic alterations, more circulatory abnormalities, and more inflammation,^(11,40) which raises the possibility of additional pathophysiological mechanisms for sleep and cognitive disturbances in these patients. These mechanisms may be important in the transition from covert to overt HE.

Our findings further our understanding of compensated cirrhosis and its substratification and provide grounds for future research and, subsequently, to clinical practice. By demonstrating greater sleep disturbances in those with CSPH, it is possible that other neurocognitive alterations would be present in this subpopulation of patients and would therefore identify them as the target population to be included in clinical studies that could predict the development of overt HE and could lead to strategies to prevent it. Additional research is also needed to understand the relationship between portosystemic collaterals and sleep disturbance as well as the quality of life impact of sleep disturbance in patients with compensated cirrhosis.

Circadian sleep-wake abnormalities⁽⁴¹⁾ may explain some of the observed association between portosystemic collaterals and greater sleep disturbance. Zee et al.⁽¹²⁾ observed alterations in the circadian rhythm and pineal melatonin content of rats subjected to portocaval anastomoses, modeling portosystemic collaterals wherein portal blood

is circulated into the systemic circulation. Delayed melatonin secretion, peak, and clearance are seen in patients with cirrhosis compared to healthy controls⁽⁴²⁻⁴⁵⁾; but delays in melatonin rhythm have not fully associated with sleep disturbance in cirrhosis.^(42,43) This may be because these prior studies combined compensated and decompensated cirrhosis in their study populations; consequently, their findings were confounded by multiple factors, including overt HE, profound liver insufficiency, discomfort from ascites, and severe illness.

Increased systemic inflammation is another plausible explanation for sleep disturbance in this population. A relationship between cytokines and sleep disturbances has been observed in study populations with and without cirrhosis.⁽¹⁴⁻¹⁷⁾ Recent observations of increased C-reactive protein in patients with clinically significant portal hypertension (compared to those without)⁽¹¹⁾ lend support to the possibility of systemic inflammation as a driver for worsened sleep disturbance associated with collaterals. Additional research that includes novel measures of inflammation is needed.

Other possible factors that may contribute to poor sleep in this population include medications, common sleep disorders, behavioral, and environmental factors. Beta-blocker medications, commonly used among patients with cirrhosis and gastroesophageal varices, are often blamed for sleep disturbance as they are associated with circadian disruption through their negative effects on melatonin levels.⁽⁴⁶⁾ However, beta-blocker use does not sufficiently explain our findings as our analysis controlled for beta-blocker usage. Undiagnosed sleep disorders may be common in this population, and future research should include a diagnostic interview for insomnia and a full-night polysomnography to assess for their presence and, in particular, obstructive sleep apnea (OSA) and restless leg syndrome.

The high levels of sleep disturbance we observed across the entire study population belie the conventional view that compensated cirrhosis is an entirely asymptomatic stage of disease. Sleep disturbance may in fact be the main and frequently underappreciated symptom of compensated cirrhosis. Moreover, and as confirmed in our study, poor sleep is a well-documented contributor to daytime symptoms and decrements in function and quality of life in many populations of chronic disease, including cirrhosis.⁽⁶⁾

In fact, our findings point to the need to 1) assess sleep in these patients and provide referral for behavioral or pharmacological sleep intervention (or maybe continuous positive airway pressure if it turns out they have sleep apnea); 2) target specific treatments to the sleep alterations. Addressing sleep may improve quality of life, symptoms, and possibly some of the inflammatory or other pathophysiological effects.

Strengths of this study include the exclusion of potential confounders including habitual alcohol, recreational drug and pharmacologic sleep aid use, uncontrolled psychiatric disease, and overt HE. We used validated sleep and sleepiness measures previously used in studies involving cirrhosis,^(18,41,47,48) performed wrist actigraphy for 7 days to account for night-to-night sleep variability,⁽⁴⁹⁾ and corroborated sleep and wake times with sleep diaries.⁽¹⁸⁾ Important to note is that actigraph measures and self-report sleep and sleepiness measures capture different aspects of sleep. Thus, the lack of correlation between the two sets of measures was expected and entirely consistent with prior observations.^(6,48) Perhaps the most important strength of this study is a homogeneous characterization of patients with compensated cirrhosis.

The primary limitation of this study was the small sample. However, this was planned as a small exploratory proof-of-concept study that would identify whether there would be a signal and, if so, to determine effect sizes for future more fully powered studies. Despite the small sample size, we did find statistically significant differences between groups in actigraph-assessed sleep characteristics and statistically significant associations between portosystemic collaterals and sleep disturbance. Although we excluded patients with sleep disorders, it is possible that the sample included patients with undiagnosed primary sleep disorders. It should be noted that BMI was not different between groups, which may ameliorate the possibility that OSA was differentially distributed between groups.

In summary, we have established that portosystemic collaterals (therefore, CSPH) are independently associated with sleep disturbances in compensated cirrhosis. To further our understanding of these disturbances and their relationship with covert HE, future studies should focus on compensated cirrhosis in order to avoid confounding from decompensations and associated liver synthetic dysfunction. The next step ought to explore the mechanism by which portosystemic collaterals lead to sleep disturbance and

potentially explore the role of circadian abnormalities, primary sleep disorders, shunted gut toxins, systemic inflammatory cytokines, and the gut microbiome. Finally, future studies are needed to further evaluate the behavioral factors that contribute to sleep disturbance in these patients, the effects of sleep disturbance on disease and quality of life outcomes, and the role of sleep interventions.

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