Fatigue and sleep quality before and after liver transplantation

Context—Recent publications suggest that fatigue and sleep disturbance are problems in patients with chronic liver disease and in liver transplant recipients.
Objectives—To characterize the severity and nature of fatigue and sleep quality before and after liver transplantation, to examine the relationship between fatigue/sleep quality and quality of life, and to identify their multivariate correlates.
Design, Settings, and Participants—Cross-sectional survey administered to 110 patients before and 95 patients after liver transplantation at 2 transplant centers.
Main Outcome Measures—Fatigue and sleep quality.
Results—Most pretransplant (86%) and posttransplant (76%) patients experienced high fatigue severity. Correlates of pretransplant fatigue severity were being female (odds ratio [OR] = 0.22, $P = .04$), higher body mass index (OR = 1.07, $P = .04$), higher mood disturbance (OR = 1.05, $P = .02$), and poor sleep quality (OR = 0.26, $P = .02$). Correlates of posttransplant fatigue severity were use of sleep medications in the past month (OR = 0.51, $P = .02$) and higher mood disturbance (OR = 1.06, $P = .004$). Seventy-three percent of pretransplant and 77% of posttransplant patients were classified as having poor sleep quality. Higher body mass index (OR = 1.06, $P = .05$), sleep medications (OR = 0.43, $P = .03$), and more mood disturbance (OR = 1.04, $P = .007$) were predictive of poor sleep quality in pretransplant patients, whereas higher body mass index (OR = 1.07, $P = .04$) and more anxious mood (OR = 1.28, $P = .03$) were predictive of poor sleep quality in posttransplant patients.
Conclusion—A very high proportion of both pretransplant and posttransplant patients experience clinically severe fatigue levels. Prospective research is necessary to identify causal mechanisms of these disorders and to evaluate strategies to reduce fatigue severity and improve sleep quality. (*Progress in Transplantation.* 2010;20:221-233)

James R. Rodrigue, PhD,
David R. Nelson, MD,
Alan I. Reed, MD,
Douglas W. Hanto, MD, PhD,
Michael Curry, MD
Beth Israel Deaconess Medical Center, Boston, Massachusetts (JRR, DWH, MC), University of Florida, Gainesville (DRN), University of Iowa, Iowa City (AIR)

Corresponding author: James R. Rodrigue, PhD, The Transplant Institute, Beth Israel Deaconess Medical Center, 110 Francis Street, LMOB-Suite 7, Boston, MA 02215
(e-mail: jrrodrig@bidmc.harvard.edu)

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Fatigue is a subjective phenomenon that can be characterized as persistent tiredness or exhaustion that is usually distressing to the person experiencing it.[1] Sleep quality also is a subjective experience, which can be affected by impaired sleep initiation, maintenance, and adequacy. Adults with chronic liver disease are likely to experience severe fatigue and associated sleep disturbances.[2,3] Despite limited evidence of a relationship between fatigue and histological features of liver disease,[3] recent research has identified fatigue severity as a primary predictor of poor quality of life (QOL) in patients with liver disease.[4-6] Sleep disturbances, including insomnia and obstructive apnea,[7,8] also are common among adults with chronic liver disease and may be associated with subclinical encephalopathy in those with cirrhosis.[9]

Although liver transplantation improves health-related QOL, evidence is emerging that fatigue remains an important clinical problem after liver transplantation. For instance, van den Berg-Emons and colleagues[10] reported that 44% of liver transplant recipients were severely fatigued, most commonly characterized by physical (as opposed to mental) fatigue. Women, older recipients, higher perceived disability, and lower health-related QOL were associated with higher fatigue severity. Aadahl et al[11] also found that physical fatigue was most prominent among those with a history of alcoholic or cryptogenic cirrhosis, unemployment, and more recent (1-3 years) liver transplantation. Sleep disturbances have not been systematically examined after liver transplantation. In their review of the literature on QOL after liver transplantation, Bravata et al[12] indicated the greatest change in QOL after liver transplantation was in energy and ability to sleep. This conclusion, however, was based on a review of 5 studies in which sleep was a small component of a more global assessment of QOL.

In previous liver transplant studies, researchers have not consistently assessed known correlates of fatigue

or sleep quality. For instance, although depression and obesity are associated with fatigue and disturbances in sleep quality,[13-15] they have not been evaluated in patients both before and after liver transplantation. Additional study of fatigue and sleep quality in the context of liver transplantation is important for several reasons. Specifically, better understanding of fatigue and sleep quality (and their correlates) before and after liver transplantation may help health professionals to better inform patients about these clinical parameters, may encourage transplant professionals to systematically assess these constructs, and may facilitate the development and implementation of specific interventions to improve fatigue severity and sleep quality. Using validated measures of fatigue and sleep quality, we sought (1) to characterize the severity and nature of fatigue and sleep quality before and after liver transplantation, (2) to assess the relationship between fatigue and sleep quality and QOL, and (3) to identify their multivariate correlates. We hypothesized that fatigue and sleep quality would be highly prevalent in patients both before and after liver transplantation, fatigue severity would be associated with low QOL, and psychological factors (eg, mood disturbance) would be predictive of fatigue and sleep disturbance severity.

Methods

Recruitment of Participants

Using a convenience sampling strategy, we recruited study participants from 2 US transplant centers: the University of Florida in Gainesville and the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts. To be eligible for the study, patients had to be at least 18 years old, able to speak and read English, provide informed consent, and either be listed for liver transplantation or be a liver transplant recipient. Also, only recipients who had received their liver transplant more than 3 months ago were included because hospital readmissions, rehabilitation needs, and medication adjustments are common during the first 3 months after transplant. Study procedures were approved by the institutional review boards of both institutions.

Assessment Protocol

Patients completed several standardized questionnaires with known validity and reliability in the assessment of fatigue, sleep quality, QOL, and mood disturbance. Questionnaires were completed in the outpatient transplant clinics. In addition, a trained research assistant collected the following information from medical records: current age, sex, race, education, marital status, employment status, current body mass index (BMI), substance abuse and smoking history, indication for liver transplantation, current calculated Model for End-Stage Liver Disease (MELD) score in patients before liver transplantation, calculated MELD score at time of transplant in liver transplant recipients, and time since liver transplantation. For the BIDMC sample, we also recorded whether the patient had an analgesic medication prescribed. This information was not gathered for the sample from the University of Florida.

Fatigue Symptom Inventory. The Fatigue Symptom Inventory (FSI)[16] is used to assess the frequency, severity, and perceived disruptiveness of fatigue. Frequency is reflected in (a) the number of days in the past week (0-7) that patients felt fatigued and (b) the percentage of each day, on average, that patients felt fatigued (0 = none to 10 = entire day). Fatigue severity is assessed by using 4 separate scales (0 = not at all fatigued to 10 = as fatigued as I could be) to measure current fatigue and the most, least, and average fatigue experienced in the past week. Perceived disruptiveness is measured by using 7 separate scales (0 = no interference to 10 = extreme interference) that assess the degree to which fatigue in the past week interfered with general activity level, concentration, relationships, enjoyment of life, and mood. These interference ratings are summed to yield a total disruptiveness score. A composite fatigue severity score for the FSI is obtained by averaging the severity items. A score of 3 or greater has been empirically identified as the cutoff for identifying clinically meaningful fatigue.[1] For the primary fatigue severity analyses in the present study, we used this clinical cutoff score.

Multidimensional Fatigue Symptom Inventory-Short Form. The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)[17] comprises 30 statements, and patients report the degree to which they have experienced each symptom in the past week (0 = not at all to 4 = extremely). Scores are then summed to assess the multidimensional nature of fatigue across 5 subscales: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor. A fatigue total score is also obtained (vigor is negatively loaded).

Pittsburgh Sleep Quality Index. The 19-item Pittsburgh Sleep Quality Index (PSQI)[18] assesses sleep quality during the past month. A global sleep quality score and 7 component scores are obtained in the following areas: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. Higher scores indicate worse sleep quality. A global sleep quality score of greater than 5 has been used as the cutoff for identifying clinically poor sleep quality.[19,20]

SF-36v2 Health Survey. The SF-36v2 Health Survey (SF-36)[21] is a generic measure of health-related QOL

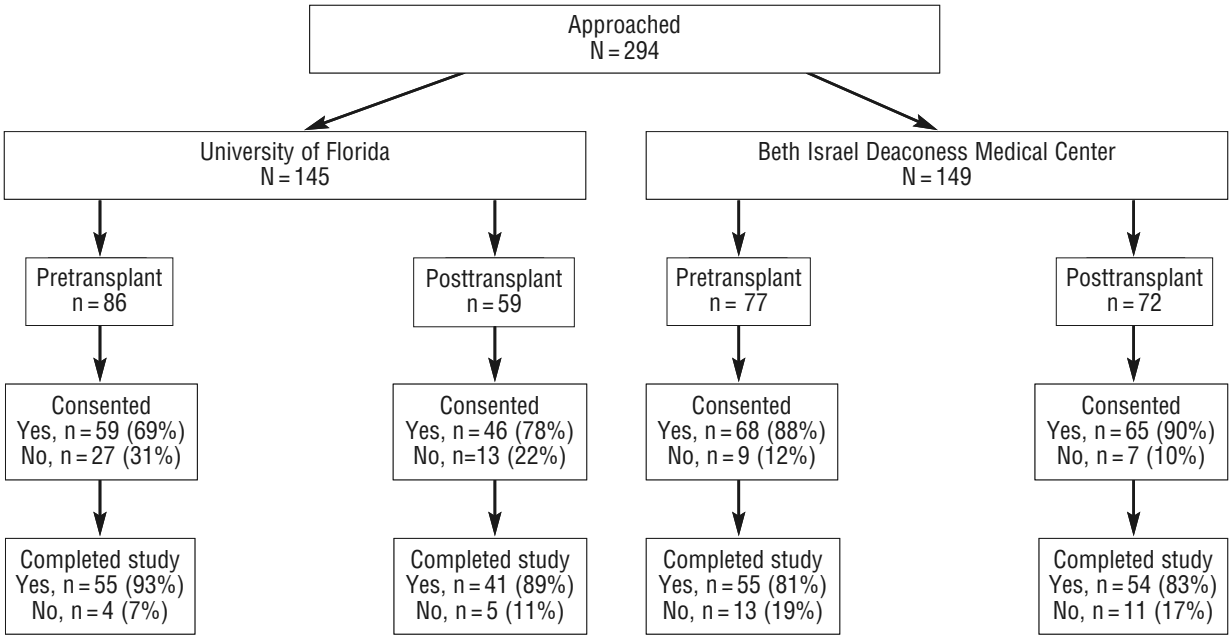

Figure 1 Summary of recruitment and enrollment of participants in study on fatigue and sleep quality before and after liver transplantation.

that is used to assess self-perceptions of health across 8 domains: physical functioning, role functioning–physical, role functioning–emotional, vitality, pain, general health, social functioning, and mental health. Scores range from 0 to 100, with higher scores reflecting higher QOL. In addition to the individual domain scores, the SF-36 yields 2 composite scores: Physical Component Summary and Mental Component Summary.

Profile of Mood States–Short Form. The Profile of Mood States–Short Form (POMS-SF)[22] is a measure of mood disturbance. Patients read descriptive adjectives and indicate on a 5-point Likert scale (0 = not at all to 4 = extremely) the extent to which they have felt that way in the past week. Item scores are summed to yield a Total Mood Disturbance score and 6 factor scores: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. With the exception of the vigor-activity score, higher scores indicate more mood disturbance.

Statistical Analysis

Preliminary analyses were conducted to examine the underlying distributional properties of all outcome variables and covariates and patterns of missing data. Missing data (3% of all data points for the current study) were replaced by using the multiple imputation strategy. Student *t* tests, Fisher exact tests, and χ^2 analyses were conducted to examine for differences in patients' sociodemographic characteristics between the 2 transplant centers. On the basis of these findings, the samples from the 2 centers were combined.

To assess the first study aim, descriptive statistics for all sample characteristics and dependent measures were calculated and expressed as means (and standard deviations) or as proportions and are described separately for pretransplant and posttransplant patients. Both parametric and nonparametric tests were used to examine differences in fatigue and sleep quality along with patients' sociodemographic and clinical characteristics. Fatigue severity (measured via the FSI) and sleep quality (measured via the PSQI) were dichotomized by using the clinical cutoffs noted earlier, and we examined the relationship between these outcome measures and patients' sociodemographic and clinical characteristics.

To assess the second study aim, those variables that were significantly associated ($P < .05$) with the outcome measures were subsequently included in multiple logistic regression analyses to identify significant correlates of fatigue severity and poor sleep quality in both pretransplant and posttransplant patients. Statistical significance was operationalized as a probability value of .05 or less; however, to reduce the risk of inflating type I error, Bonferroni correction was applied when multiple comparisons were made within a particular variable. All analyses were conducted by using SPSS 16.0 for Windows (SPSS Inc, Chicago, Illinois).

Results

Study Enrollment

Study enrollment is highlighted in Figure 1. The most common reasons for not participating in the study

were lack of interest and time constraints while attending the transplant clinics. Not all patients who consented to be in the study completed the questionnaires. In most instances (88%), this situation occurred because they provided consent to be in the study while in the waiting room, subsequently were called back to see their transplant physician, and then left the clinic before completing the questionnaires (eg, to get laboratory tests done, to pursue additional clinical testing, to see another provider, or to go home). Overall, 96 patients (55 pretransplant, 41 posttransplant) at the University of Florida and 109 patients (55 pretransplant, 54 posttransplant) at BIDMC completed data collection, yielding a total sample of 110 pretransplant patients and 95 posttransplant patients. Those who completed the study questionnaires were significantly younger ($P = .03$) than those who consented but did not complete data collection, although no other sociodemographic features differed between these 2 groups.

Sample Characteristics

Except for current time on the liver transplant waiting list (pretransplant patients) and calculated MELD score at the time of transplant (posttransplant patients), the University of Florida and BIDMC samples did not differ significantly in sociodemographic characteristics and dependent measures. Relative to patients at BIDMC, pretransplant patients at the University of Florida had a lower mean number of days on the liver transplant waiting list (520.3, SD 130.2 vs 190.3, SD 53.6; $t = 6.1$, $P < .001$) and posttransplant patients at the University of Florida had a lower mean calculated MELD score at the time of liver transplantation (22.3, SD 10.3 vs 17.8, SD 6.9; $t = 3.7$, $P = .02$). Patients from the 2 centers were combined for all subsequent analyses.

Pre- and posttransplant patients' characteristics are summarized in Table 1. Most patients in both the pretransplant group and the posttransplant group were male, white, unemployed, married, had a smoking history, and had infection with hepatitis C virus or alcohol abuse as the cause of their primary liver disease.

Pretransplant Fatigue and Sleep Quality

Fatigue Frequency and Severity. Most patients (n = 103, 94%) reported having experienced at least 1 day of fatigue during the past week. Mean (SD) number of days of fatigue in the past week was 4.80 (2.2), with more than half (n = 62, 60%) reporting 5 or more days of fatigue. On average, they reported feeling fatigued 50% of the day. Using the composite FSI fatigue severity score cutoff of 3 or greater, 95 (86%) patients reported clinically high fatigue severity. Forty percent of patients with fatigue could not identify a consistent pattern of fatigue, although fatigue was generally worse in the afternoon (23%) or evening (20%) than in the morning (16%).

Nature of Fatigue. Mean (SD) scores for the different dimensions of fatigue on the MFSI-SF are illustrated in Figure 2. The mean scores differed significantly from each other (all P values $< .01$), with mean scores for general and physical fatigue significantly higher than those for emotional and mental fatigue.

Fatigue Interference. FSI responses showed that 96 patients (87%) experienced fatigue interference in 1 or more areas of daily functioning. Fatigue interference was significantly higher for general activity (mean 4.32, SD 3.2) and mood (mean 3.96, SD 3.3) than for self-care activities (2.07, SD 2.8), concentration (mean 3.19, SD 2.9), or relationships with others (mean 3.21, SD 3.2) (all P values $< .01$).

Sleep Quality. Mean (SD) global PSQI score was 8.94 (4.6), which is greater than the clinical cutoff that indicates poor sleep quality (ie, PSQI score > 5). When this clinical cutoff score was used, 80 patients (73%) were classified as having poor sleep quality. Mean (SD) length of time to fall asleep at night was 35.4 (37.3) minutes, and mean (SD) number of hours of sleep per night was 6.6 (1.4). Most patients (n = 94, 85%) reported having trouble staying asleep because of waking up during the night. The most common reasons for nighttime awakening were going to the bathroom (82%), pain (52%), body temperature dysregulation (42%), and coughing or snoring loudly (31%). Forty-one patients (37%) had used sleep medications during the past month, with 24 of them (59%) using such medication 3 or more times per week.

Posttransplant Fatigue and Sleep Quality

Fatigue Frequency and Severity. Almost all patients (n = 89, 94%) had experienced at least 1 day of fatigue during the past week. Mean (SD) number of days of fatigue in the past week was 4.72 (2.1), with 65% (n = 58) reporting 5 or more days of fatigue. Seventy-two patients (76%) had clinically high fatigue severity indicated by the composite FSI fatigue severity score cutoff of 3 or greater. More than one-third (38%) reported no discernable pattern of fatigue; however, half (49%) stated that fatigue was worse in the afternoon or evening.

Nature of Fatigue. Mean (SD) MFSI-SF scores are presented in Figure 3. Mean scores for general and physical fatigue were significantly higher than mean scores for mental fatigue (all P values $< .001$).

Fatigue Interference. Eight-eight patients (93%) reported that fatigue interfered with at least 1 area of daily functioning, as shown by responses to the FSI. Fatigue interference was significantly higher for general activity (mean 4.28, SD 3.0), work (mean 4.04, SD

Table 1 Sociodemographic and clinical characteristics of pre- and posttransplant patients

Characteristic	Pretransplant patients (n = 110)	Posttransplant patients (n = 95)
Age, y	52.1 ± 8.1	55.0 ± 10.0
Gender, female, No. (%)	49 (45.5)	37 (38.9)
Race, No. (%)		
White	95 (86.4)	80 (84.2)
Black	6 (5.5)	6 (6.3)
Hispanic	5 (4.5)	4 (4.2)
Other	4 (3.6)	5 (5.3)
Education, No. (%)		
<High school	14 (12.7)	6 (6.3)
High school graduate	79 (71.8)	60 (63.2)
College graduate	17 (15.5)	29 (30.5)
Married, No. (%)	57 (51.8)	57 (60.0)
Employed, No. (%)	35 (31.8)	34 (35.8)
Body mass index	28.4 ± 6.1	27.1 ± 5.1
Alcohol abuse/dependence history, No. (%)	45 (40.9)	50 (52.6)
Drug abuse/dependence history, No. (%)	40 (36.4)	34 (35.8)
Cigarette smoking in past 3 mo, No. (%)	63 (57.3)	64 (67.4)
Disease etiology (primary), No. (%)		
Hepatitis C virus	55 (50.0)	49 (51.5)
Alcohol	38 (34.5)	34 (35.8)
Nonalcoholic steatohepatitis	5 (4.6)	3 (3.2)
Autoimmune hepatitis	3 (2.7)	2 (2.1)
Primary biliary cirrhosis	4 (3.6)	3 (3.2)
Hepatocellular carcinoma	5 (4.6)	4 (4.2)
Hepatocellular carcinoma, No. (%)	25 (22.7)	29 (30.5)
Pretransplant decompensation, No. (%)		
Ascites	51 (46.4)	
Hepatic encephalopathy	38 (34.5)	
Variceal bleeding	14 (12.7)	
Calculated MELD score	16.0 ± 9.4[a]	19.3 ± 9.4[b]
Waiting time, d	302.2 ± 322.5	
Survival, d		760.8 ± 593.3

Abbreviation: MELD, Model for End-Stage Liver Disease.
[a] Calculated at time of study participation.
[b] Calculated at time of liver transplant.

3.1), and enjoying life (mean 3.84, SD 3.0) than for self-care activities (mean 1.76, SD 2.5) or relationships with others (mean 3.07, SD 2.8) (all P values < .01).

Sleep Quality. The mean (SD) global PSQI score of 9.68 (4.1) exceeded the clinical cutoff (score >5) for poor sleep quality, and 73 patients (77%) met this criterion for poor sleep quality. Mean (SD) length of time to fall asleep at night was 37.7 (28.9) minutes, and mean (SD) number of hours sleep per night was 6.6 (1.8). Most patients (n = 79, 83%) reported nighttime awakening, including going to the bathroom (90%), pain (44%), and coughing or snoring loudly (34%). Fifty-nine patients (62%) had used sleep medications during the past month, with 29 of them (49%) using such medications 3 or more times per week.

Fatigue, Sleep Quality, and QOL

The associations between the SF-36 QOL domains and both fatigue severity (FSI score ≥3) and sleep quality (PSQI score >5) were examined separately for pretransplant and posttransplant patients. Results were essentially identical, and the 2 samples were combined for ease of illustration. Figure 4 shows that high fatigue severity was associated with significantly compromised scores on most SF-36 domains, and Figure 5 shows that poor sleep quality was associated with more bodily pain.

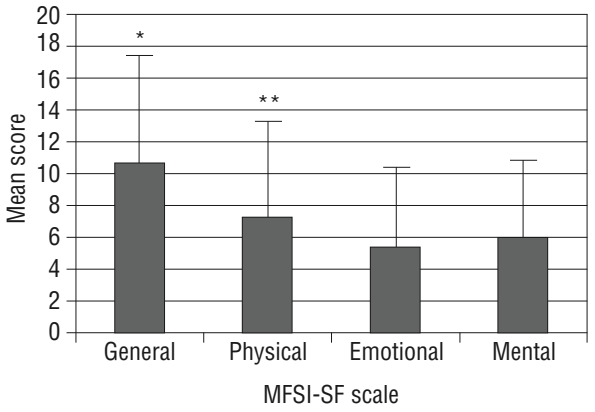

Figure 2 Nature of pretransplant fatigue as measured by the Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF). Higher scores reflect more fatigue.

* Score significantly higher than scores on physical ($t = 7.7$, $P < .001$), emotional ($t = 8.8$, $P < .001$), and mental ($t = 8.4$, $P < .001$) scales.
** Score significantly higher than scores on emotional ($t = 4.2$, $P < .001$) and mental ($t = 3.1$, $P = .007$) scales.

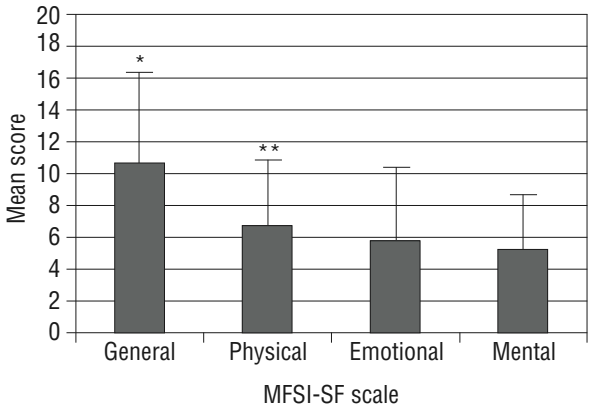

Figure 3 Nature of posttransplant fatigue as measured by the Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF). Higher scores reflect more fatigue.

* Score significantly higher than scores on physical ($t = 7.9$, $P < .001$), emotional ($t = 8.6$, $P < .001$), and mental ($t = 9.5$, $P < .001$) scales.
** Score significantly higher than score on mental ($t = 3.9$, $P < .001$) scale.

Sociodemographic and Clinical Correlates of Fatigue Severity and Sleep Quality

The sociodemographic and clinical characteristics and their relationship to fatigue severity and sleep quality for pretransplant and posttransplant patients are displayed in Tables 2 and 3, respectively. For pretransplant patients, unemployment, higher BMI, higher calculated MELD score, and use of sleep medication in the past month were significantly associated with both high fatigue severity and poor sleep quality. Also, being female and having poor sleep quality were significantly associated with high fatigue severity, whereas a history of alcohol dependency, a history of variceal bleeding, being prescribed analgesic medication, more depressed and anxious mood, more anger, and high fatigue severity were significantly related to poor sleep quality.

For posttransplant patients, no sociodemographic characteristics were significantly associated with either fatigue severity or sleep quality. Patients with high fatigue severity were significantly more likely to have been taking sleep medication in the past month and have more total mood disturbance than do patients with low fatigue severity. Patients with poor sleep quality were significantly more likely to have a higher BMI and to be prescribed analgesic and sleep medications than were patients with good sleep quality.

Correlates of Fatigue Severity and Poor Sleep Quality

Four separate logistic regression analyses were conducted to examine the relative contribution of sociodemographic and clinical characteristics correlated with fatigue severity and sleep quality for both pretransplant and posttransplant patients. Only those variables that were previously shown to be statistically associated with fatigue severity or sleep quality (described above) were included in the analysis. Results of the regression analyses are summarized in Table 4.

Statistically significant multivariable correlates of high fatigue severity before liver transplantation were higher BMI and higher total mood disturbance; male sex and good sleep quality were associated with reduced risk of fatigue problems. In pretransplant patients, poor sleep quality was associated with higher BMI and higher total mood disturbance; no use of sleep medications in the past month was associated with reduced risk of problems with sleep quality.

After liver transplantation, high fatigue severity was associated with use of sleep medications in the past month and higher total mood disturbance. Significant correlates of poor sleep quality after liver transplantation were higher BMI and more anxious mood.

Discussion

This study is the first to simultaneously examine fatigue severity and sleep quality in a cross-sectional cohort of patients both before and after liver transplantation from 2 transplant centers. Study strengths include the use of well-validated assessments, a high participation rate, and the examination of factors known to be associated with fatigue and sleep disturbance. Overall, the study had 4 major findings: (1) a very high proportion of both pretransplant and posttransplant patients experience clinically severe fatigue levels, (2) sleep quality is equally poor in pretransplant

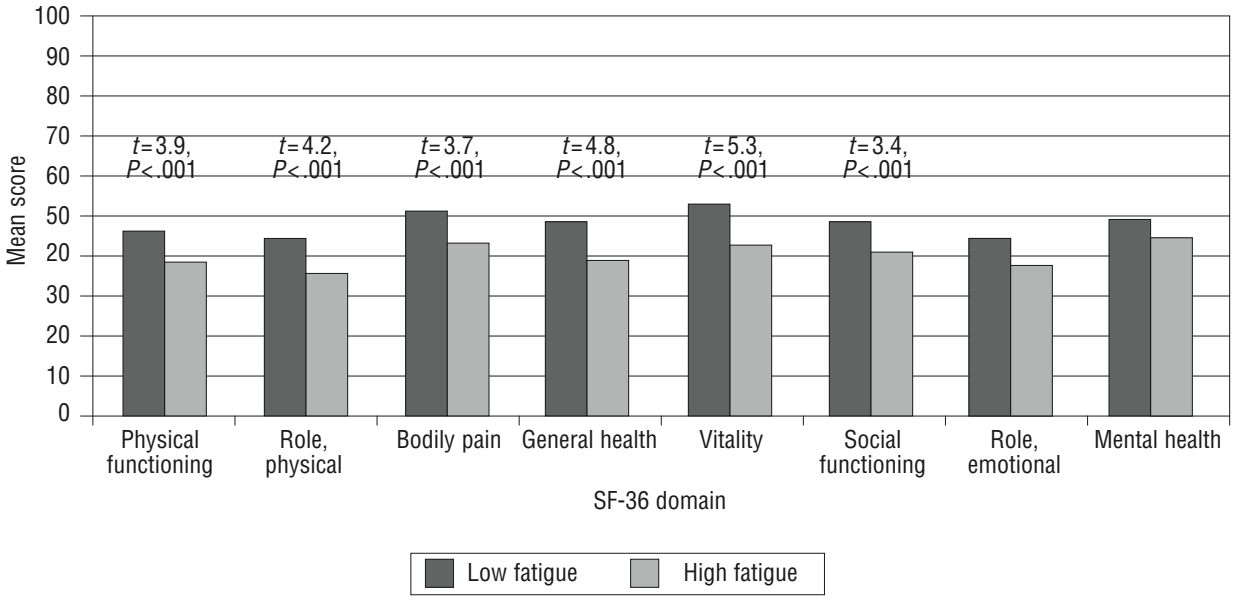

Figure 4 Relationship between fatigue severity and quality of life for pretransplant and posttransplant samples combined. Higher scores reflect better quality of life. Fatigue Symptom Inventory clinical cutoff of 3 of greater was used to classify patients as having low (n = 38) versus high (n = 167) fatigue.

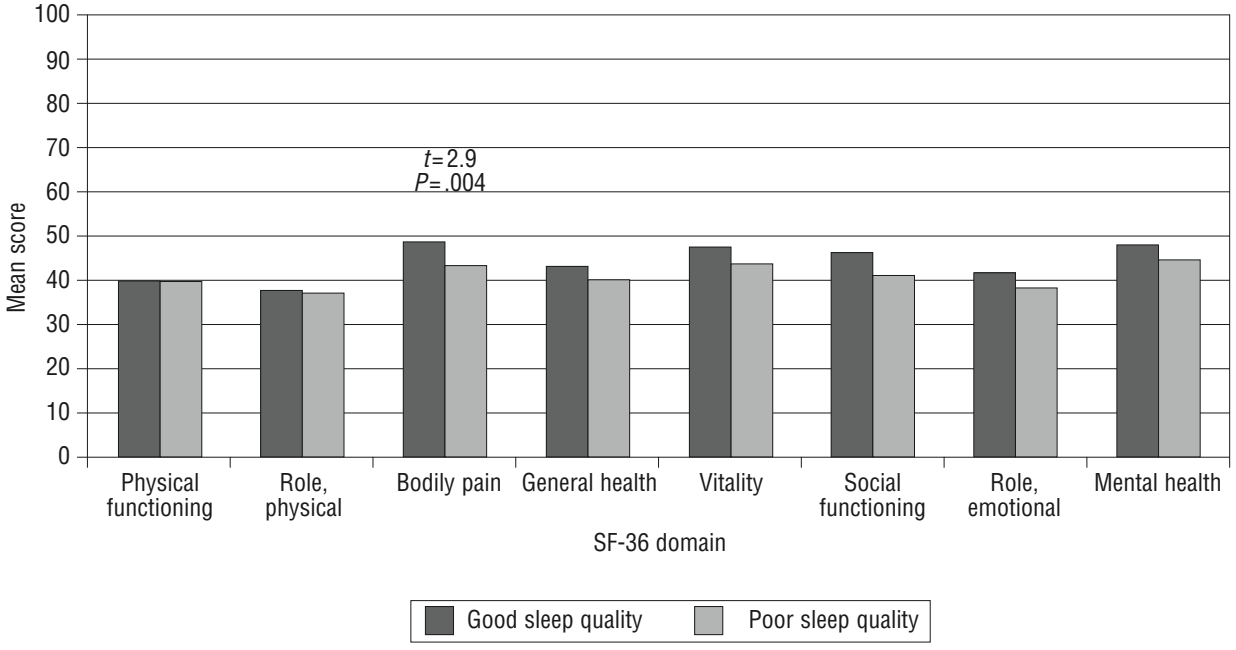

Figure 5 Relationship between sleep quality and quality of life for pretransplant and posttransplant samples combined. Higher scores reflect better quality of life. Pittsburgh Sleep Quality Index clinical cutoff of 5 or greater was used to classify patients as having good (n = 52) versus poor (n = 153) sleep quality.

patients and posttransplant patients, (3) high fatigue severity and poor sleep quality both are associated with lower QOL for both pretransplant and posttransplant patients, and (4) higher BMI and more mood disturbance are salient correlates of pretransplant and posttransplant fatigue and sleep problems.

We found an alarmingly high proportion of patients with clinically significant fatigue severity and sleep disturbances. Fatigue is a major symptom associated with several chronic liver diseases, including nonalcoholic steatohepatitis, primary biliary cirrhosis, and hepatitis C.[2-7] Indeed, Gross et al[23] reported that fatigue was the most frequent and distressing symptom for patients before transplantation. Using a more comprehensive fatigue assessment model, we also found that the vast majority of patients in our pretransplant

Table 2 Pretransplant sociodemographic and clinical characteristics: univariate associations with fatigue severity and sleep quality (n = 110)

	Fatigue severity					Sleep quality				
	Low (n = 15)		High (n = 95)		*P*	Good (n = 30)		Poor (n = 80)		*P*
Sociodemographic characteristic										
Age, mean (SD), y	52.5	(5.1)	52.0	(8.5)	.81	51.4	(10.5)	52.3	(7.1)	.62
Gender, No. (%)										
Female	2	(13.3)	47	(49.5)	.008	11	(36.7)	38	(47.5)	.39
Male	13	(86.7)	48	(50.5)		19	(63.3)	42	(52.5)	
Race, No. (%)										
White	14	(93.3)	81	(85.3)	.40	25	(83.3)	70	(87.5)	.57
Other	1	(6.7)	14	(14.7)		5	(16.7)	10	(12.5)	
Education, No. (%)										
<High school	3	(20.0)	11	(11.6)		4	(13.3)	10	(12.5)	
High school graduate	10	(66.7)	69	(72.6)	.66	20	(66.7)	59	(73.8)	.70
College graduate	2	(13.3)	15	(15.8)		6	(20.0)	11	(13.7)	
Marital status, No. (%)										
Married	9	(60.0)	49	(51.6)	.54	15	(50.0)	43	(53.7)	.73
Not married	6	(40.0)	46	(48.4)		15	(50.0)	37	(46.3)	
Employed, No. (%)										
Yes	9	(60.0)	26	(27.4)	.02	14	(46.7)	21	(26.2)	.04
No	6	(40.0)	69	(72.6)		16	(53.3)	59	(73.8)	
Clinical characteristic										
Body mass index, mean (SD)	26.2	(5.8)	30.2	(6.9)	.04	27.0	(6.5)	29.6	(6.0)	.05
Alcohol abuse/dependency, No. (%)										
Yes	7	(46.7)	38	(40.0)	.78	6	(20.0)	39	(48.8)	.006
No	8	(53.3)	57	(60.0)		24	(80.0)	41	(51.2)	
Drug abuse/dependency, No. (%)										
Yes	6	(40.0)	34	(35.8)	.78	13	(43.3)	27	(33.8)	.38
No	9	(60.0)	61	(64.2)		17	(56.7)	53	(66.2)	
Cigarette smoking in past 3 mo, No. (%)										
Yes	9	(60.0)	54	(56.8)	.99	17	(56.7)	46	(57.5)	.99
No	6	(40.0)	41	(43.2)		13	(43.3)	34	(42.5)	
Disease etiology (primary), No. (%)										
Hepatitis C	3	(20.0)	52	(54.7)		16	(53.3)	39	(48.8)	
Alcohol	4	(26.7)	34	(35.8)		5	(16.7)	33	(41.3)	
Nonalcoholic steatohepatitis	2	(13.3)	3	(3.2)	.001	2	(6.7)	3	(3.7)	.06
Autoimmune hepatitis	2	(13.3)	1	(1.1)		2	(6.7)	1	(1.2)	
Primary biliary cirrhosis	0	(0.0)	4	(4.2)		2	(6.7)	2	(2.5)	
Hepatocellular carcinoma	4	(26.7)	1	(1.1)		3	(10.0)	2	(2.5)	
Hepatocellular carcinoma, No. (%)										
Yes	2	(13.3)	23	(24.2)	.51	6	(20.0)	19	(23.8)	.80
No	13	(86.7)	72	(75.8)		24	(80.0)	61	(76.2)	
Ascites, No. (%)										
Yes	6	(40.0)	45	(47.4)	.78	13	(43.3)	38	(47.5)	.83
No	9	(60.0)	50	(52.6)		17	(56.7)	42	(52.5)	
Hepatic encephalopathy, No. (%)										
Yes	3	(20.0)	35	(36.8)	.25	8	(26.7)	30	(37.5)	.37
No	12	(80.0)	60	(63.2)		22	(73.3)	50	(62.5)	
Variceal bleeding, No. (%)										
Yes	2	(13.3)	12	(12.6)	.99	0	(0.00)	14	(17.5)	.03
No	13	(86.7)	83	(87.4)		30	(100.0)	66	(82.5)	
Calculated MELD, mean (SD)	13.2	(5.8)	18.9	(9.9)	.03	13.1	(5.2)	17.0	(10.3)	.05
Wait-listed time, mean (SD), d	319.8	(158.8)	299.5	(271.3)	.78	374.6	(389.5)	275.1	(183.6)	.07
Prescribed analgesia,[a] No. (%)										
Yes	3	(27.3)	23	(52.3)	.14	1	(12.5)	25	(53.2)	.03
No	8	(72.7)	21	(47.7)		7	(87.5)	22	(46.8)	

Continued

Table 2 *Continued*

Clinical characteristic	Fatigue severity			Sleep quality		
	Low (n = 15)	High (n = 95)	*P*	Good (n = 30)	Poor (n = 80)	*P*
Taking sleep medication in past month, No. (%)						
Yes	2 (13.3)	39 (41.1)	.04	2 (6.7)	37 (46.3)	.001
No	13 (86.7)	56 (58.9)		28 (93.3)	43 (53.7)	
Mood disturbance,[b] mean (SD)						
Depression	1.7 (2.1)	4.6 (4.7)	.02	2.4 (3.4)	4.9 (4.8)	.01
Anxiety	2.5 (2.9)	3.7 (3.2)	.17	2.4 (2.7)	4.0 (3.2)	.02
Anger	2.8 (2.7)	4.6 (3.7)	.07	2.6 (2.4)	5.1 (3.8)	.001
Total mood disturbance	5.9 (13.9)	18.9 (20.2)	.02	8.4 (14.6)	20.4 (20.7)	.004
Sleep quality,[c] No. (%)						
Good	8 (53.3)	22 (23.2)	.02			
Poor	7 (46.7)	73 (76.8)				
Fatigue severity,[d] No. (%)						
Low				8 (26.7)	7 (8.8)	.02
High				22 (73.3)	73 (91.1)	

Abbreviation: MELD, Model for End-Stage Liver Disease.
[a] This information was available only for a subsample of patients (n = 55).
[b] Profile of Mood States-Short Form.
[c] Determined by a Pittsburgh Sleep Quality Index global cutoff score of >5.
[d] Determined by a Fatigue Symptom Inventory composite fatigue severity score of ≥3.

sample had severe fatigue. Moreover, fatigue was multidimensional and included physical, emotional, and mental fatigue. It is important for clinicians to recognize that fatigue extends beyond the physical manifestations of chronic illness, including changes in cognitive functioning (eg, disruption in concentration, attention, and memory processes) and the psychological stress associated with waiting for a transplant. Pretransplant patients are required to assimilate, retain, and remember a great deal of information about their illness and its management, and they must successfully navigate a very complex transplant clinical pathway at a time when their neurocognitive resources are more limited. These efforts can lead to extreme levels of mental and emotional fatigue.

Numerous studies have documented the QOL benefits associated with liver transplantation.[23-26] However, our study highlights that fatigue is a prominent symptom for many posttransplant patients and that low QOL in some areas is associated with high fatigue levels and poor sleep quality. This finding is consistent with results of other studies, including van den Berg-Emons et al,[10] who reported a fatigue prevalence rate of 66% among liver transplant recipients. High fatigue severity is associated with patients' sense of physical well-being, role responsibilities, social functioning, and perceptions about whether liver transplantation was successful.

More than two-thirds of study patients reported sleep disturbances. Again, this finding is not surprising for pretransplant patients, because obstructive sleep apnea, fragmented nocturnal sleep, reversal of sleep rhythm, and prolonged napping time are commonly seen in adults with chronic liver disease.[7,8,24-29] Córdoba et al[30] reported that 48% of patients with cirrhosis (n = 44) without hepatic encephalopathy experienced unsatisfactory sleep. In a case control study with a larger sample size (n = 178), Mostacci et al[31] found that patients with cirrhosis had significantly higher rates of poor sleep quality (28% vs 8%), daytime sleepiness (49% vs 22%), and habitual napping (55% vs 23%) than did healthy control subjects matched for age and sex. Fewer patients are taking sleep medication before liver transplantation, compared with after liver transplantation, perhaps because of concerns about worsening encephalopathic symptoms.

However, patients (and perhaps their providers) often express the expectation that liver transplantation will lead to improvements in sleep quality. Our data suggest that sleep quality is problematic after liver transplantation. The most common sleep problems identified by pretransplant patients—sleep latency (55%), sleep disturbances (55%), and daytime dysfunction (42%)—were also those most commonly reported by posttransplant patients (57%, 63%, and 41%, respectively). Of course, given the cross-sectional design, we cannot comment on whether sleep quality improves or deteriorates from before to after liver transplantation. The mechanisms underlying sleep disturbances may be different from before to after liver transplantation,

Table 3 Posttransplant sociodemographic and clinical characteristics: univariate associations with fatigue severity and sleep quality (n = 95)

	Fatigue severity			Sleep quality		
	Low (n = 23)	High (n = 72)	*P*	Good (n = 22)	Poor (n = 73)	*P*
Sociodemographic characteristic						
Age, mean (SD), y	57.0 (10.5)	54.4 (9.8)	.28	56.8 (8.5)	54.5 (10.4)	.34
Gender, No. (%)						
Female	6 (26.1)	31 (43.1)	.22	7 (31.8)	30 (41.1)	.47
Male	17 (73.9)	41 (56.9)		15 (68.2)	43 (58.9)	
Race, No. (%)						
White	17 (73.9)	63 (87.5)	.12	21 (95.5)	59 (80.8)	.10
Other	6 (26.1)	9 (12.5)		1 (4.5)	14 (19.2)	
Education, No. (%)						
<High school	2 (8.7)	4 (5.6)		2 (9.1)	4 (5.4)	
High school graduate	18 (78.3)	42 (58.3)	.11	12 (54.6)	48 (65.8)	.61
College graduate	3 (13.0)	26 (36.1)		8 (36.3)	21 (28.8)	
Marital status, No. (%)						
Married	12 (52.2)	45 (62.5)	.38	13 (59.1)	44 (60.3)	.92
Not married	11 (47.8)	27 (37.5)		9 (40.9)	29 (39.7)	
Employed, No. (%)						
Yes	11 (47.8)	23 (31.9)	.21	9 (40.9)	25 (34.2)	.62
No	12 (52.2)	49 (68.1)		13 (59.1)	48 (65.8)	
Clinical characteristic						
Body mass index, mean (SD)	26.9 (4.1)	27.2 (5.4)	.80	25.5 (4.4)	28.3 (5.3)	.03
Alcohol abuse/dependency, No. (%)						
Yes	11 (47.8)	39 (54.2)	.64	10 (45.5)	40 (54.8)	.47
No	12 (52.2)	33 (45.8)		12 (54.5)	33 (45.2)	
Drug abuse/dependency, No. (%)						
Yes	9 (39.1)	25 (34.7)	.80	6 (27.3)	28 (38.4)	.45
No	14 (60.9)	47 (65.3)		16 (72.7)	45 (61.6)	
Cigarette smoking in past 3 mo, No. (%)						
Yes	14 (60.9)	50 (69.4)	.46	15 (68.2)	49 (67.1)	.99
No	9 (39.1)	22 (30.6)		7 (31.8)	24 (32.9)	
Disease etiology (primary), No. (%)						
Hepatitis C	8 (34.8)	41 (56.9)		9 (40.9)	40 (54.8)	
Alcohol	9 (39.1)	25 (34.7)		9 (40.9)	25 (34.3)	
Nonalcoholic steatohepatitis	1 (4.4)	2 (2.8)	.22	2 (9.1)	1 (1.4)	.11
Autoimmune hepatitis	1 (4.4)	1 (1.4)		0 (0.0)	2 (2.7)	
Primary biliary cirrhosis	2 (8.7)	1 (1.4)		2 (9.1)	1 (1.4)	
Hepatocellular carcinoma	2 (8.7)	2 (2.8)		0 (0.0)	4 (5.5)	
Calculated MELD at transplant, mean (SD)	22.0 (9.8)	18.6 (9.5)	.15	17.6 (6.8)	19.9 (10.0)	.33
Time since transplant, No. (%)						
<1 year	5 (21.7)	24 (33.3)		6 (27.3)	23 (31.5)	
1-2 years	6 (26.1)	21 (29.2)	.10	6 (27.3)	21 (28.8)	.64
3-5 years	12 (52.2)	20 (27.8)		7 (31.8)	25 (34.2)	
>5 years	0 (0.0)	7 (9.7)		3 (13.6)	4 (5.5)	
Immunosuppression,[a] No. (%)						
Tacrolimus	9 (60.0)	22 (56.4)		9 (64.3)	22 (55.0)	
Sirolimus	6 (40.0)	16 (41.0)	.89	5 (45.7)	17 (42.5)	.61
Tacrolimus and sirolimus	0 (0.0)	1 (2.6)		0 (0.0)	1 (2.5)	
Prescribed analgesia,[a] No. (%)						
Yes	8 (57.1)	25 (62.5)	.72	4 (28.6)	29 (72.5)	.003
No	6 (42.9)	15 (37.5)		10 (71.4)	11 (27.5)	
Taking sleep medication in past month, No. (%)						
Yes	10 (43.5)	49 (68.1)	.03	9 (40.9)	50 (68.5)	.02
No	13 (56.5)	23 (31.9)		13 (59.1)	23 (31.5)	

Continued

Table 3 *Continued*

	Fatigue severity			Sleep quality		
	Low (n = 23)	High (n = 72)	*P*	Good (n = 22)	Poor (n = 73)	*P*
Clinical characteristics						
Mood disturbance,[b] mean (SD)						
Depression	3.1 (2.8)	4.1 (4.1)	.26	3.2 (3.8)	4.1 (3.8)	.31
Anxiety	2.7 (2.4)	4.1 (2.8)	.04	2.7 (2.2)	4.1 (2.8)	.03
Anger	3.2 (2.7)	4.5 (3.5)	.13	3.4 (2.8)	4.4 (3.5)	.23
Total mood disturbance	6.6 (13.5)	19.5 (17.5)	.002	11.1 (15.5)	18.0 (17.7)	.10
Sleep quality,[c] No. (%)						
Good	6 (26.1)	16 (22.2)	.78			
Poor	17 (73.9)	56 (77.8)				
Fatigue severity,[d] No. (%)						
Low				6 (27.3)	17 (23.3)	.78
High				16 (72.7)	56 (76.7)	

Abbreviation: MELD, Model for End-Stage Liver Disease.
[a] This information was available only for a subsample of patients (n = 55).
[b] Profile of Mood States-Short Form.
[c] Determined by a Pittsburgh Sleep Quality Index global cutoff score of >5.
[d] Determined by a Fatigue Symptom Inventory composite fatigue severity score of ≥3.

but the high prevalence rates underscore the importance of routine assessments of sleep quality before and after liver transplantation. Although several sleep assessment methods are available for this purpose (eg, single-item and visual analogue scales, sleep logs, and sleep diaries), we recommend using the PSQI because it is easy to administer, brief, well validated, widely used in medical populations, and it measures several components of sleep quality.

Higher BMI and more mood disturbance were significantly correlated with fatigue severity and poor sleep quality. The rising incidence of obesity in adults presenting for liver transplantation and among liver transplant recipients is of concern because obesity is an independent risk factor for obstructive sleep apnea, insomnia, and fatigue.[15,32-35] Also, obese adults are less likely to engage in regular physical activity, which may also contribute to fatigue severity, excessive daytime sleepiness, and reduced sleep quality.[15] Weight loss interventions for liver transplant patients, in addition to reducing morbidity and mortality risks,[32] may improve self-reported fatigue and sleep quality. Fatigue and sleep disturbances are core symptoms of major depression and anxiety,[13,14] conditions known to be common in liver transplant patients.[36,37] The finding that total mood disturbance is associated with fatigue severity and poor sleep quality both before and after liver transplantation highlights the importance of assessing and managing psychological symptoms.

Reported findings on the relationship between disease parameters and fatigue are conflicting. Aadahl et al,[11] for instance, found that liver transplant recipients with alcoholic or cryptogenic cirrhosis and who had received a transplant 1 to 3 years earlier had more physical fatigue than did patients with other diagnoses or longer time since receiving the transplant. In contrast, van den Berg-Emons et al[10] failed to show any association between indication for liver transplant, time since liver transplant, and fatigue severity. In our study, cause of disease was significantly associated with pretransplant (but not posttransplant) fatigue severity in the univariate analysis, although most of our study patients had hepatitis C or alcohol-related liver disease, and this variable was not significant in the final multivariable regression analysis. Similarly, although MELD score and variceal bleeding met statistical significance in the univariate analyses, they also were not retained in the regression analyses. It is also noteworthy that fatigue and sleep quality did not differ on the basis of the patient's immunosuppression regimen. It may be that these particular clinical parameters are not as salient in determining fatigue severity and sleep disturbance as other characteristics, including BMI and mood disturbance.

No randomized clinical trials have been done to examine the effectiveness of strategies to manage or limit the impact of fatigue and sleep disturbances in liver transplant patients. Ian Gan et al[38] reported that 31 of 42 adults with primary biliary cirrhosis reported increased energy, decreased somnolence, and improved daily function during a 3-day trial of 100 to 200 mg modafinil, with 25 patients continuing to take modafinil months later with good resolution of fatigue. However, that article describes their clinical experience and was not intended to describe results of a research study, and the authors did not use validated measures

Table 4 Results of multivariable logistic regression analysis for fatigue severity and sleep quality, broken down by pre- and posttransplant patients

Variables	Odds ratio	*P*	95% CI
Pretransplant patients			
High fatigue severity[a,b]			
Male sex	0.22	.04	0.06-0.83
Higher body mass index	1.07	.04	1.01-1.18
Total mood disturbance (POMS-SF)	1.05	.02	1.01-1.09
Good sleep quality	0.26	.02	0.09-0.81
Poor sleep quality[c,d]			
Higher body mass index	1.06	.05	1.01-1.17
No sleep medication in past month	0.43	.03	0.18-0.77
Total mood disturbance (POMS-SF)	1.04	.007	1.01-1.07
Posttransplant patients			
High fatigue severity[a,e]			
No sleep medication in past month	0.51	.02	0.33-0.81
Total mood disturbance (POMS-SF)	1.06	.004	1.02-1.10
Poor sleep quality[c,f]			
Higher body mass index	1.07	.04	1.01-1.19
Anxious mood (POMS-SF)	1.28	.03	1.02-1.61

Abbreviations: CI, confidence interval; POMS-SF, Profile of Mood States-Short Form.

[a] High fatigue severity is defined as Fatigue Symptom Inventory composite score of ≥3.
[b] Total model is significant ($P = .003$) and the Hosmer-Lemeshow test showed good model fit ($\chi^2 = 6.0$, $P = .65$) with high discrimination (0.86).
[c] Poor sleep quality is defined as Pittsburgh Sleep Quality Index global score of >5.
[d] Total model is significant ($P = .02$) and the Hosmer-Lemeshow test showed good model fit ($\chi^2 = 5.2$, $P = .74$) with high discrimination (0.79).
[e] Total model is significant ($P = .01$) and the Hosmer-Lemeshow test showed good model fit ($\chi^2 = 7.9$, $P = .45$) with high discrimination (0.77).
[f] Total model is significant ($P = .05$) and the Hosmer-Lemeshow test showed good model fit ($\chi^2 = 2.5$, $P = .13$) with high discrimination (0.79).

of fatigue or sleep disturbance. Nevertheless, those data are promising and certainly suggest the need for a more rigorous clinical trial. Many different reasons can explain the paucity of empirically evaluated interventions for fatigue in liver transplant patients. First, no general guidelines or standard care practices exist for the management of fatigue or sleep disturbances in this population. Second, different underlying mechanisms may cause different fatigue symptoms or sleep disturbances. For instance, preexisting comorbid medical or psychiatric conditions, impaired cognitive function, alterations in central neurotransmission, desynchronization of the circadian system, metabolic syndrome, recurrent disease, pharmacological agents, and a sedentary lifestyle may all contribute differently to the presentation of fatigue or to the nature of sleep disturbances. Thus development and evaluation of interventions are difficult. Nevertheless, rehabilitation programs targeting physical fitness, obesity management, and optimal psychological adjustment may lead to moderate improvements in fatigue symptoms or sleep quality and also might provide substantial QOL benefits. Also, whenever possible, transplant programs should establish clinical collaborations with sleep health clinics to coordinate the screening, assessment, and treatment of fatigue and sleep-related disturbances identified in the current study, as well as other sleep-related problems that are common in liver transplant patients (eg, insomnia, obstructive sleep apnea).

Study findings should be evaluated within the context of a few methodological limitations. We used a cross-sectional design, which did not allow us to assess how fatigue or sleep quality changes over time. More prospective studies are needed. Also, although patients were recruited from 2 transplant programs, findings may not generalize to all patients before and after liver transplantation. Indeed, a self-selection bias is inherent in any study of this nature. Patients most affected by fatigue or poor sleep quality may have been more likely to participate in the study, thus skewing the data toward higher prevalence rates. We did not corroborate self-reported data by using objective measures (eg, actigraphy to monitor rest/activity cycles), although previous studies have shown a strong association between these 2 methods.[30] Finally, we did not assess for factors found by other researchers to be associated with fatigue, including anemia, serum levels of sodium, and immunosuppressant agents.[11,39,40]

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