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Poor Sleep in Organ Transplant Recipients: Self-Reports and Actigraphy

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Abstract

Solid organ transplant recipients are at increased risk for poor sleep due to pharmacotherapy and co-morbidities, but sleep problems are often unrecognized and untreated. Study aims were to measure rates of occurrence, characteristics and correlates of poor sleep in recipients. The Pittsburgh Sleep Quality Index (PSQI) and sleep parameters measured by wrist actigraphy were obtained at baseline from 143 kidney, liver, heart, lung or pancreas transplant recipients enrolled in a psychosocial intervention trial to improve symptoms and quality of life. Rates of poor sleep were determined using accepted clinical cut-offs; 41% (58 of 143) were poor sleepers (PSQI >8) and 36% used sleep medications in the past month. 15% reported having obstructive sleep apnea and 4% reported restless legs syndrome. Based on actigraphy (n=73), 69% lacked sleep efficiency; 32% took greater than 30 minutes to fall asleep; 88% awakened during the night for more than 30 minutes; and 25% slept less than 6 hours per night. Obesity and use of psychotropics or sleep medications were independent risk factors for poor objectively-measured sleep. Poor sleep is an undertreated problem in transplantation. Screening for sleep problems and behavioral therapies with sleep hygiene instruction may benefit recipients.

Introduction

While organ transplant is frequently life-saving and a treatment of last resort, the effects of surgery and the medical management of organ recipients often result in new or recurrent problems. Immunosuppressive side effects, complications, rejection, and the manifestations of end-organ disease have serious quality-of-life consequences, and sleep problems are particularly common and problematic. Sleeplessness is among the most frequently reported side effects of steroids and immunosuppressive medications (1) and is associated with non-adherence (2). Symptoms such as pain and itching may also reduce sleep quantity and quality. Sleep difficulties commonly co-occur with symptoms of fatigue, depression and anxiety (3), symptoms prevalent among transplant recipients (4-6). Sleep problems vary in frequency and in level of distress, by medication and by recipient variables. In transplant recipients, estimates of sleep problems vary widely. In recent studies of renal transplant recipients, prevalence rates for poor sleep ranged from 30% (N=100) (7) to 62% (N=125) (8) based on the Pittsburgh Sleep Quality Index (PSQI).

Sleep is unique among quality of life variables in that it can be measured both subjectively and objectively. Sleep dysfunction may be defined using specific diagnostic criteria, i.e. obstructive sleep apnea (OSA); parameters from polysomnography or actigraphy; by standardized self-report scales (such as the PSQI); or as self-reported sleep problems. Sleep problems have gained national attention due to serious health consequences such as depression, diminished quality of life and premature mortality, and major economic consequences including increased health care utilization and lost productivity (9). There is also considerable evidence that sleep problems are generally under-diagnosed and not

effectively treated (10). One in five people in the general population report insomnia (the most common sleep disorder), with higher rates among women, older adults and those with chronic health problems (11). Pharmacotherapy, either prescription or over-the-counter sleep aids, is the most common treatment for insomnia, however medications do not address the underlying causes of insomnia, and for transplant recipients, these ancillary medications contribute to polypharmacy, raising risks of medication errors and non-adherence.

The purpose of this study was to investigate the prevalence, characteristics, and correlates of sleep difficulties in solid organ transplant recipients. Based on the literature, it was anticipated that rates of poor sleep would vary by age, gender, type of transplant, use of psychotropic or sleep medications, and co-morbidities. It was also expected that sleep quality would have moderate to strong correlations with symptoms of depression, anxiety, fatigue, and pain. We also examined relationships between lifestyle factors of obesity, lack of exercise, and use of nicotine, alcohol, and caffeine. To explore the potential value of assessing self-reported sleep difficulty in clinical practice, we examined the agreement between self-reported and actigraphy-derived sleep parameters, and identified risk factors for both objectively and subjectively determined poor sleep.

Methods

Participants

Participants were adult, solid-organ transplant recipients enrolled in a randomized controlled trial of mindfulness training versus chronic disease self-management education to improve symptoms and enhance quality of life. Participants had functioning grafts, were receiving standard medical care, and were at least 6 months from time of their most recent transplant surgery. There were no sleep-related inclusion or exclusion criteria. Participants were recruited between 2003 and 2007, using brochures and posters in transplant clinic waiting areas, presentations to transplant advocacy groups, and through letters from physicians. Details of the study are presented elsewhere (12).

Of the 150 recipients who consented to be in this trial, 143 provided self-reported sleep data at pre-intervention baseline. Seventy-three recipients also provided baseline actigraphy data. There were fewer participants in the actigraphy component of the study because it was introduced after the first series of recipients had completed baseline data collection, and some participants (e.g., shiftworkers) were excluded from actigraphy. The flow of participants in this study is shown in Figure 1.

Measures

Self-reported Sleep

Sleep quality in the past month was assessed by the Pittsburgh Sleep Quality Index (PSQI) which has been validated and used in a variety of clinical populations. A psychometric evaluation of the PSQI with four clinical samples, including renal transplant recipients, demonstrated good internal consistency (Cronbach's $\alpha = .80$) and good construct validity (13). The PSQI includes 19 questions to assess 7 domains of sleep: sleep quality, latency (time to fall asleep), duration, efficiency (the ratio of sleep duration by time in-bed), disturbances (e.g. getting up to use the bathroom), use of sleep medications, and daytime dysfunction. Sleep domains are scored 0-3; global PSQI scores range from 0-21 with a cut-off score of >5 indicating poor sleep in the general population and a recommended cut-off score of >8 identifying poor sleep among people with chronic health conditions (13, 14).

Objectively Measured Sleep

Actigraphy is a means of collecting objective sleep/wake data in the natural sleep environment over an extended period of time, whereas polysomnography takes place in a medical setting, is costly, and sleep assessment over many nights is not feasible (15). An actigraph is a motion-sensing accelerometer the size of a wristwatch. Study participants wore a wrist actigraph on their non-dominant wrist, or on their dominant wrist if they had a fistula, and completed a daily sleep diary for up to two weeks at baseline. Data from the actigraphs were downloaded into a computer and the following sleep parameters were estimated: total sleep time (TST), sleep onset latency (SOL), wake after sleep onset (WASO), and sleep efficiency (SE) - time asleep divided by time in bed (Actiwatch® AW64 analyzed by Actiware Sleep v.3.4 software, Mini-Mitter Company, Inc., a Philips-Respironics Company, Bend, Oregon). Benchmarks for poor sleep are SOL or WASO of greater than 30 minutes, total sleep time of less than six hours and sleep efficiency less than 85% (15).

Demographics, clinical characteristics and symptoms

Demographics, health history and lifestyle variables (use of nicotine, alcohol, caffeine) were collected by interview at the informed consent visit. Obesity was calculated by Body Mass Index (BMI) (Formula: Weight (lbs) / height (in)² × 703), based on self-reports at enrollment. BMI was categorized into four groups: underweight defined as a BMI less than 18.5; normal weight defined as a BMI of at least 18.5 but less than 25; overweight defined as a BMI of at least 25 but less than 30; and obese defined as a BMI of 30 or higher per The Centers for Disease Control and Prevention (CDC, 2012) (16).

Four sentinel symptoms – anxiety, depression, fatigue and pain - were assessed using standardized, validated scales that have been previously used with transplant recipients. Anxiety was measured by the State-Trait Anxiety Inventory - State Version (STAI) (17); depression was measured by the Center for Epidemiological Studies - Depression Scale (CES-D) (18); and fatigue (energy/vitality) and pain were measured with Short-Form 36 version 2 (SF-36) subscales (19). Pain and vitality are standardized T-scores (mean=50, standard deviation=10), where 50 is the general adult population average or norm, and higher scores indicate better outcomes (less pain, more vitality).

Analyses

Participant demographics and clinical characteristics, their self-reported sleep quality, and actigraphy-based sleep parameters were summarized using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences among recipients grouped by transplanted organ, or between those with self-report and self-report plus actigraphy were compared using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Associations between self-reported sleep and other symptom scales were assessed using Pearson correlations. Agreement between self-reported sleep and actigraphy findings was evaluated using Bland-Altman (20). Results were considered statistically significant at $p < 0.05$.

Risk factors for poor sleep determined by self-report and by actigraphy were identified using hierarchical multivariate logistic regression. These analyses were conducted in stages. First, potential risk factors were screened for an association with poor sleep using t -tests or chi-square tests conducted at the $p < 0.10$ level. Factors that passed screening were then divided into demographics, clinical, and lifestyle variables. First, demographic variables were entered into the model and significant predictors retained for subsequent steps. Next, clinical variables were added to the model to assess the impact of clinical factors on poor sleep, after controlling for demographics, and significant clinical factors retained. Lifestyle variables

were then added to determine their incremental impacts on poor sleep, after controlling for demographics and clinical variables. We termed this model 1. As there is overlap between PSQI and measures of depression, anxiety and pain, sentinel symptoms were added in our second and final model. For self-report regressions, both the whole sample (n=143) and the kidney recipient subgroup (n=77) were examined. Smaller sample sizes precluded additional regressions by organ type.

For the actigraphy regressions, any variable that screened positively for univariate association with any dependent variable (SOL, TST, and SE) was entered for each of the three regressions. Odds ratios (ORs) and 95% CIs were estimated for each risk factor. The final model was selected using log-likelihood test statistics and the pseudo-R² (scores range from 0 to 1, higher is stronger). Model fit was evaluated by Hosmer-Lemeshow tests (p values below 0.05 indicate lack of fit). All statistical analyses were conducted using SPSS 19.0 (SPSS Inc., Chicago, IL).

Protection of Human Subjects

This study was approved by the Institutional Review Boards of the University of Minnesota and Hennepin County Medical Center. All enrolled participants attended an informational interview about the study and signed an informed consent.

Results

Characteristics of the Sample

Recipients (N=143) ranged in age from 21 to 75 years old (average age 54 years), and there were slightly more men (55%) than women. Kidney recipients comprised about half the sample (77 out of 143). Several demographic variables differed by type of transplant (Table 1). The heart transplant recipients were generally older (average age 64) and the kidney/pancreas recipients, younger (average age 48). Most of the kidney/pancreas recipients were women (75%), whereas 85% of heart recipients were men. Roughly half of all recipients were currently working full or part-time, with the highest rate of employment among the kidney/pancreas recipients (69%) and the lowest (23%) among the heart recipients, many of whom were retired. Time since transplant surgery ranged from 6 months to over 33 years, with a median of 3.8 years. The lung recipients were closest to time of surgery (mean = 3.4 years) and the heart recipients had the longest average times (over 9 years) from transplant surgery.

Recipients reported a substantial chronic disease burden. Over half the sample (54%) and almost all kidney/pancreas recipients (88%) reported at least four co-morbidities, and nearly half (47%) of the sample had used psychotropic or sedative hypnotic medications for sleep, anxiety or depression in the past month. Many clinical and transplant-specific factors differed by organ transplant type in a manner consistent with commonly reported causes of organ failure.

Lifestyle factors were not significantly different across groups. Very few were current cigarette smokers (about 5%), and most exercised at least occasionally (85%). The majority of the recipients were overweight or obese (38% and 21%, respectively), and approximately one fourth (24.5%) of the sample reporting drinking three or more caffeinated beverages every day.

Self-reported sleep problems

Poor sleep was common in all transplant groups; there were no significant differences by transplant type for the PSQI scores, overall or by component (Table 2). Based on the PSQI

cutoff of greater than 8 for people with chronic diseases, 41% of recipients were poor sleepers. By the general population criterion of a PSQI greater than 5, 65% of recipients were poor sleepers. Substantial proportions of recipients exceeded consensus benchmarks for poor sleep: 35% reported taking more than 30 minutes to fall asleep at bedtime; 21% reported sleeping fewer than 6 hours a night; 57% lacked sleep efficiency (were sleeping less than 85% of the time they were in bed trying to sleep, based on PSQI).

About one out of three recipients (36%) reported using sleep medications at least once in the last month, and major sleep impairments were not rare: 18% reported taking more than an hour to fall asleep at bedtime; 10% regularly slept fewer than 5 hours a night; and 19% reported taking sleep medications 3 or more nights a week in the past month. Rates of diagnosed sleep disorders, however, were modest. About 15% of recipients reported having been diagnosed with OSA and only 4% reported having restless legs syndrome (RLS).

The PSQI includes standard reasons for poor sleep and the following percentages reflect the proportion of our sample who reported these problems at least 3 nights per week in the past month: have to get up to use the bathroom (67%), wake up in the middle of the night or early morning (58%), cannot get to sleep within 30 minutes (19%), have pain (17%), cough or snore loudly (15%), feel too hot (13%), feel too cold (10%), cannot breathe comfortably (6%), or had bad dreams (6%). A space is also provided for handwritten other reasons. Thirty-nine percent of recipients reported other reasons, and we divided these responses into common themes. The most common were descriptions of types of pain (30%), anxiety or worry (25%), or hyperarousal (e.g. mind-racing, inability to “wind down”) (18%). Environmental disruptions (snoring bed partner, attending to pets) or failure to abide by sleep hygiene practices (going to bed too late, napping) each represented 11% of comments. Seven percent of recipients described symptoms of chronic insomnia, e.g. “never had a good night's sleep since my 20s,” and 5% reported ongoing disruption from OSA or RLS. Remaining reasons were itching (n=1 liver recipient) and recent grief (n=1).

Risk factors for self-reported poor sleep

Risk factors for poor sleep defined by a PSQI score above 8 are shown in Table 3. Variables identified by univariate screening to be related ($p < 0.10$) to poor self-reported sleep included: female gender, married, college or higher post-graduate education, muscular comorbidity, OSA, use of sedatives or psychotropic medications in the last month, current full- or part-time employment, or lack of exercise. Multivariate analysis revealed two significant, independent factors: use of sedatives or psychotropic drugs in the last month as a risk factor, and full or part-time employment as a protective factor for poor sleep. Recipients using sedatives or psychotropics were over 7 times more likely to report poor sleep than those not using these drugs (OR = 7.69, 95% CI: 3.46 - 17.11, $p < .001$). Conversely, recipients currently working were about 60% less likely to report poor sleep (OR = 0.37, 95% CI: 0.17 - 0.83, $p < 0.05$). In model 2, sentinel symptoms were included to assess their contributions to poor sleep outcomes. Anxiety and fatigue were found to be significant risk factors (OR = 1.07, CI: 1.01 – 1.14, $p < 0.05$; OR = 1.06, CI: 1.00 – 1.13, $p < 0.05$, respectively) for self-reported poor sleep, and the clinical and lifestyle factors from model 1 remained significant.

Kidney recipients (n=77) were evaluated in regression models 1 and 2, to examine whether the relationships observed for the whole sample would be demonstrated for this more homogenous subgroup. In model 1, independent risk factors for poor sleep included use of medications (OR = 11.93, CI = 3.76 – 37.88, $p < 0.001$) and lack of exercise (OR = 6.91, CI: 1.06 – 45.19, $p < 0.05$). As for the whole sample, model 2 was stronger, and use of medications was the highest risk factor, representing 16-17 times risk (OR = 16.51, 95% CI: 3.05 – 89.29, $p < 0.01$), but lack of exercise was no longer significant, and fatigue emerged as a new risk factor (OR = 1.17, CI: 1.04 – 1.33, $p < 0.05$).

Associations between self-reported sleep and symptoms

Moderately strong correlations were found between self-reports of sleep on the PSQI and symptoms of depression (CES-D), anxiety (STAI), fatigue (SF-36), and pain (SF-36), with Pearson r 's of 0.61, 0.58, -0.58 and -0.49, respectively (p 's <0.001, all). These correlations represent shared variance in the range of 25%-36% between sleep and these symptoms. The relationships were all in the expected direction – worse sleep and more depression symptoms, more anxiety, more fatigue and more pain (SF-36 values are reverse coded, e.g., higher scores are less fatigue, less pain). As all these symptoms were measured at the same point in time, causal relationships cannot be inferred. However, as noted above, recipients were asked about specific reasons for their sleep difficulties, and common problems included early waking, pain, and anxiety or hyperarousal.

Actigraphy findings

Recipients ($n=73$) wore wrist actigraphs to objectively estimate sleep parameters. Actigraphs were worn for an average of 11 nights, and 83.6% wore actigraphs for at least 7 nights. The demographics, clinical and lifestyle factors were compared between those with and without actigraphy. These factors were generally well-balanced, with the following exceptions. The actigraphy sample had a lower proportion of kidney transplant recipients (44% vs. 64%: $p=0.01$), proportionately fewer individuals who reported drinking 3 or more caffeinated beverages a day (16% vs. 33%: $p=0.02$), and somewhat higher proportions of women (52% vs. 37%: $p=0.11$) and individuals with neurologic co-morbidities (48% vs. 33%: $p=0.07$).

Actigraphy confirmed high rates of sleep dysfunction across all transplant recipient groups (Table 4). 25% of the actigraphy sample slept fewer than 6 hours nightly and 32% took more than 30 minutes to fall asleep at bedtime. Average sleep efficiency was only 80%, and 88% of recipients were awake during the night for more than 30 minutes after sleep onset. Time to fall asleep (sleep onset latency, SOL) was the only actigraphy parameter to vary significantly by type of transplant, with liver recipients taking about 45 minutes to fall asleep at bedtime (Figure 2).

Risk factors for poor sleep measured by actigraphy

Three actigraphy-derived benchmarks for poor sleep were examined: sleep onset latency of greater than 30 minutes ($SOL > 30$ min.); duration of total sleep time of less than 6 hours ($TST < 6$ hr.); and lack of sleep efficiency ($SE < 85\%$). Variables identified by univariate screening to be related ($p < 0.10$) to these actigraphy benchmarks included: muscular comorbidity, skeletal comorbidity, diabetes, having four or more comorbidities, OSA, kidney transplant, use of sedatives or psychotropic medications in the last month, overweight, obesity, lack of exercise, and employed full or part-time. Table 5 shows the independent risk factors for objectively measured poor sleep revealed by multivariate analyses. In Model 1, use of sedatives or psychotropics increased risk of excessively long SOL ($OR = 6.76$, 95% CI: 1.94-23.52, $p < 0.01$), obesity increased risks to poor sleep for all indicators, having a kidney transplant (compared to other types was slightly protective for TST ($OR = 0.25$, CI: 0.07 – 0.88, $p < 0.05$), pain tripled the risk for inadequate TST ($OR = 3.35$, CI: 0.96 – 11.66, $p = 0.58$), and being employed was slightly protective for SE ($OR = 0.17$, CI: 0.05 – 0.54) (data not shown). Our final model, which included sentinel symptoms of anxiety, depression, fatigue and pain, was stronger. Those who used psychotropic or sleep medications in the past month were almost 8 times more likely to exceed the actigraphy benchmark for extended SOL ($OR = 7.81$, 95% CI: 1.86 – 32.82, $p < 0.01$) than those who did not use these medications. Obesity was an independent risk factor in the final models for each of the actigraphy-defined poor sleep outcomes. Obese recipients were more than 8 times more likely to have poor total sleep time than those not obese ($OR = 8.20$, 95% CI: 1.69 – 39.92, $p < 0.01$), and the risks associated with obesity for extended SOL and reduced

total sleep time were in the magnitude of 5-6 times risk. Recipients with more pain were at higher risk of insufficient total sleep time (OR = 1.11, CI: 1.02 – 1.21, $p < 0.05$). Kidney recipients were less likely than other organ recipients to sleep fewer than 6 hours a night (OR = 0.25, 95% CI: 0.07-0.88, $p < 0.05$), and those working full or part-time were less likely than other recipients to lack sufficient sleep efficiency (OR = 0.16, CI: 0.04 – 0.59, $p < 0.01$).

Comparisons between self-report and actigraphy

Average total sleep durations measured by PSQI and actigraphy were quite comparable, 6.78 hours and 6.65 hours, respectively. Average sleep onset latencies were also similar, 29.82 minutes and 28.2 minutes for the PSQI and actigraphs, respectively. However, correlations between PSQI scores and actigraphy for TST and SOL were not strong (Spearman's $\rho = 0.376$, $p < 0.01$ and Spearman's $\rho = 0.25$, $p < 0.05$, respectively). Benchmarks for poor sleep measured by self-report and actigraphy were compared by raw agreement and Kappa statistics (21). Self-report PSQI cut-off scores of > 5 and > 8 were examined. For PSQI > 5 , raw agreements were 47% (TST < 6 hrs), 59% (SOL > 30 mins), 71% (WASO > 30 mins) and 63% (SE $< 85\%$). For PSQI > 8 , raw agreements were 52% (TST < 6 hrs), 70% (SOL > 30 mins), 49% (WASO > 30 mins) and 55% (SE $< 85\%$). Statistically significant agreement was found only for SOL and WASO - those variables directly related to being awake in bed. Kappa statistics were significant and indicated slight agreement for SOL > 30 mins for both PSQI cut-points (kappa = 0.098, PSQI > 5 ; kappa = 0.137, PSQI > 8 , $p = 0.003$, all), and for WASO > 30 mins with PSQI > 5 (kappa = 0.225, $p = 0.021$), with fair agreement. Bland-Altman plots for TST and SOL showed no systematic biases of under- or over-reporting (e.g., the average error was close to 0), but large discrepancies occurred in both directions (data not shown).

Discussion

Despite the myriad manifestations of organ failure and comorbidities in our mixed sample of organ recipients, they share the burden of poor sleep. We found that 41% (PSQI > 8) to 65% (PSQI > 5) of recipients were poor sleepers. These findings are largely consistent with published reports. Average PSQI scores for our kidney recipients (mean = 7.6 ± 4.2 ; 42% PSQI > 8 ; are very close to the averages for kidney transplant recipients from the study by Carpenter and colleagues; means of 7.9 ± 4.5 (female), 7.3 ± 4.3 (male) (13). Our finding that 72% of liver recipients were poor sleepers (PSQI > 5), was nearly identical to the 73% rate found for 95 liver recipients (PSQI > 5) in a recent study (22).

This study provides new objective data to expand understanding of sleep problems after transplant. Our actigraphy study is the largest we know of with solid organ recipients. Notably, nearly all recipients were awake for more than 30 minutes after sleep onset (i.e. were awake in the middle of the night or early in the morning) and one-third took more than 30 minutes to fall asleep. While total sleep time was adequate on average, poor sleep efficiency reveals that recipients were in bed for a long time in order to be able to achieve sufficient sleep time, thereby reducing the opportunity to engage in other activities. Sleep efficiency as calculated from self-report values, was insufficient in the majority (57%) of our sample. Wrist actigraphy confirmed high rates of sleep impairment, ranging from 25% for inadequate total sleep time to 88% for excessive wake after sleep onset. Contrary to our expectations, age, gender, and medical comorbidities were not independent risk factors for poor sleep. Statistically significant differences were not found between organ transplant groups, except that liver recipients had excessively long sleep onset latencies by actigraphy, averaging nearly 45 minutes, somewhat higher than the 38 minutes shown by Rodrigue and colleagues (2010), and having a kidney transplant, compared to other types, was slightly protective for self-reported sleep and total sleep time by actigraphy. Use of sedative or

psychotropic medications independently predicted poor sleep for self-report and actigraphy sleep onset latency. This is not surprising for the PSQI, since use of such medications contributes to the PSQI score, but actigraphy is completely independent of medication use. As such, our actigraphy analyses confirm that the self-reported use of sedatives or psychotropic medications is not resulting in good sleep outcomes.

As hypothesized, we found strong relationships between sleep and sentinel symptoms of depression and anxiety using well-validated, self-report tools, and these findings are consistent with others (22, 23). Use of psychotropic and sedative-hypnotic medications in our sample was frequent, and our data overall suggest that pharmacotherapy for sleep, anxiety, and mood disorders is inadequate or ineffective for some recipients.

Sentinel symptoms were risk factors for poor sleep, independent of use of sedatives or psychotropic medications. Anxiety and fatigue predicted poor sleep by self-report; pain predicted poor sleep measured by actigraphy. Closer examination of kidney recipients as a homogeneous group with respect to organ type underscored the risk of use of sedatives or psychotropic medications for self-reported poor sleep, and that sentinel symptoms, e.g. fatigue, increase the risk of poor sleep in recipients.

Consistent with previous reports comparing self-report and actigraphy parameters, correlations between self-report and actigraphy sleep parameters were not high (24), but Bland Altman plots demonstrated no systematic bias between the two approaches, supporting the validity of group averages based on self-report. Our comparison of these approaches demonstrates better agreement for parameters related to being awake in bed, and less agreement for parameters requiring the participant to estimate time spent sleeping. Our actigraphy results support the use of the PSQI global score with transplant recipients as a valid representation of their overall sleep quality and quantity.

Obesity, a modifiable risk factor, was a strong and independent predictor of poor sleep for all actigraphy criteria (SOL, TST, and SE). Higher BMI has previously been shown to be predictive of poor sleep quality in liver recipients (22). Obesity has consistently been identified as the strongest risk factor for OSA, and weight loss has been shown to reduce the apnea-hypopnea index (25).

While transplant recipients are at risk for sleep-disordered breathing, and OSA is a known contributor to poor sleep, only 15% of our whole sample reported a diagnosis of OSA. In a recent study of 100 kidney recipients, 25% demonstrated moderate to severe obstructive sleep apnea (OSA) based on overnight polysomnography (26). Given that the majority of our sample was overweight or obese, and given the high rate of cardiovascular disorders, our sample appears to be under diagnosed with respect to sleep-disordered breathing (SDB). In our sample, rates of OSA were higher in lung (17%) and heart recipients (23%), but still below expectations. Others report that SDB is common in as many as 62% of lung recipients one or more years post-transplant as it may recur in tandem with increases in blood pressure and BMI (27) or emerge as a new problem (28). It has been hypothesized that OSA may contribute to coronary allograft vasculopathy - a form of atherosclerosis that is the leading cause of death for heart recipients after the first year post-transplant (29).

In our sample, reports of diagnosed RLS were also infrequent and considerably lower than in the published literature. In kidney patients, RLS symptoms are associated with uremia and generally disappear following renal transplant but may recur following organ transplant due to immunosuppression nephrotoxicity (30). In this population RLS is associated to having more comorbidities, with higher risk of clinical insomnia and reduced quality of life (31), premature discontinuation of dialysis and mortality (32). In a cross-sectional study, 4.8% of renal transplant recipients (N=959) had RLS (33), about twice the rate in our sample. In our

sample, only 25% of lung recipients reported diagnosed RLS, in comparison to 48% (N=42) screened with a validated self-report tool where RLS was found to be related to female gender, higher serum calcium levels, or being recipient or donor positive for cytomegalovirus (34).

This study demonstrates that organ recipients are very concerned about pain in relation to sleep. Pain concerns were the most frequent handwritten comments on the PSQI, and reported as related to having trouble sleeping at least three times each week by 17% of recipients. Pain scale (SF-36) scores were correlated with poor sleep, and pain was a significant independent risk factor for objectively measured total sleep time. While the origin of pain in our participants was not systematically assessed, muscular and skeletal comorbidities were frequently reported, and the literature reports the high prevalence of neuropathic and osteoporotic origins among transplant recipients. Patients with diabetic peripheral neuropathy, the most common form in this population, have reported worse sleep than patients with other chronic pain conditions including postherpetic neuralgia (35), report worse pain at night, and 95% of those with moderate to severe pain report sleep disturbance (36). Even for diabetic patients who receive a pancreas transplant, restoration of peripheral nerve function is partial, with less improvement for recipients with advanced neuropathy, and may take up to 10 years (37). Recipients of other solid organs or who do not have diabetes are at risk for pain since headache and osteoporosis are common side effects of immunosuppression (1, 38).

Limitations of our study include a smaller sample size for actigraphy data. It is possible that a larger actigraphy sample may have revealed additional risk factors for poor sleep. Also, we are unable to provide evidence of the specific roles of antidepressants, anxiolytics, or sedative-hypnotics as risk factors for poor sleep since we did not verify self-reported medications, drug classes, or purposes. Nevertheless, the reported use of these medications, as a whole, was found to be related to worse, not better sleep. Comorbidities were assessed by interview and not verified against medical records. Participants were not successive admissions, but volunteers in a randomized controlled trial of mind-body therapies, which limits the ability to generalize to all recipients in the clinic.

Recommendations for clinical practice include incorporating questions about sleep into routine post-transplant follow-up care or use of the PSQI as a screening tool for global sleep problems, especially for patients who take sedative or psychotropic medications or report sentinel symptoms of pain, anxiety or fatigue, or who are overweight or obese. It should not be assumed that a prescription for sleep medication is effective. Recipients who are overweight or obese should be advised to lose weight and be educated about the relationship between obesity and sleep-disordered breathing, and possibly referred for evaluation for sleep-disordered breathing due to the high rates of OSA reported in the literature. Recipients may require interventions for pain that disrupts sleep. Provision of sleep hygiene guidelines, e.g. *Your Guide to Healthy Sleep* (NIH) (39), or recommendations for cognitive behavioral therapy or mind-body therapies for sleep or for pain may be useful tools to improve sleep in solid organ recipients.

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* Some individuals were excluded for multiple reasons.

Figure 1.
Participant flow

Figure 2.

Actigraphy sleep parameters of TST, SE and WASO did not differ across transplant groups (n=73, ANOVAs), but SOL did differ, with liver recipients taking longer to fall asleep (ANOVA, $p=0.014$). The overall proportion of patients requiring more than 30 minutes to fall asleep was 31.5%; however the proportion among liver recipients was 40%.

Table 1

Demographic and clinical characteristics of patients by transplant type (n=143)

	All (n=143)	Lung or double lung (n=12)	Liver (n=25) ^a	Kidney (n=77)	Heart (n=13) ^a	Kid/panc or pancreas (n=16)	Between-group sig.
Age (years), mean ± SD (range)	53.7 ± 10.9 (21.3-76.0)	54.1 ± 6.8 (38.7-62.1)	51.7 ± 9.3 (21.3-72.3)	53.6 ± 11.8 (23.3-75.0)	64.2 ± 8.6 (45.0-76.0)	48.1 ± 8.0 (33.5-64.4)	**
Female, n (%)	65 (45.5)	7 (58.3)	13 (52.0)	31 (40.3)	2 (15.4)	12 (75.0)	*
Non-white, n (%)	12 (8.4)	1 (8.3)	2 (8.0)	6 (7.8)	1 (7.7)	2 (12.5)	0.982
Married, n (%)	87 (60.8)	7 (58.3)	16 (64.0)	49 (63.6)	8 (61.5)	7 (43.8)	0.671
Employment: Full or part-time, n (%)	77 (53.8)	6 (50.0)	10 (40.0)	47 (61.0)	3 (23.1)	11 (68.8)	*
Education: College or post-graduate, n (%)	84 (58.8)	6 (50.0)	15 (60.0)	46 (59.8)	8 (61.6)	9 (56.3)	0.928
Years since first transplant, mean ± SD	6.5 ± 6.4	3.4 ± 3.5	4.5 ± 4.9	7.2 ± 7.1	9.5 ± 6.1	5.9 ± 5.1	0.053
Comorbidities by system, n (%)							
Cardiovascular	96 (67.1)	6 (50.0)	12 (48.0)	54 (70.1)	13 (100)	11 (68.8)	*
Respiratory	29 (20.3)	12 (100.0)	5 (20.0)	8 (10.4)	3 (23.1)	1 (6.3)	0.000
Nervous	58 (40.6)	4 (33.3)	10 (40.0)	23 (29.9)	8 (61.5)	13 (81.3)	**
Muscular	19 (13.3)	2 (16.7)	4 (16.0)	6 (7.8)	5 (38.5)	2 (12.5)	0.051
Skeletal	70 (49.0)	7 (58.3)	12 (48.0)	36 (46.8)	8 (61.5)	7 (43.8)	0.813
Digestive	59 (41.3)	6 (50.0)	24 (96.0)	16 (20.8)	4 (30.8)	9 (56.3)	0.000
Genitourinary	119 (83.2)	6 (50.0)	14 (56.0)	77 (100.0)	6 (46.2)	16 (100.0)	0.000
Diabetic	50 (35.0)	3 (25.0)	8 (32.0)	18 (23.4)	5 (38.5)	16 (100.0)	0.000
Immune	43 (30.1)	3 (25.0)	7 (28.0)	20 (26.0)	9 (69.2)	4 (25.0)	*
4 comorbidities, n (%)	78 (54.5)	8 (66.7)	13 (52.0)	33 (42.9)	10 (76.9)	14 (87.5)	0.005
Use of medications for sleep, anxiety or depression in last month, n (%)	66 (46.5)	6 (50.0)	15 (60.0)	30 (39.5)	6 (46.2)	9 (56.3)	.405
Peri- or post-menopause, n (%)	49 (75.4)	5 (71.4)	11 (84.6)	24 (77.4)	2 (100.0)	7 (58.3)	0.703
BMI, mean ± SD	26.9 ± 5.8	24.9 ± 4.1	26.7 ± 5.4	27.0 ± 5.2	30.6 ± 8.2	25.5 ± 6.8	0.100
Overweight, n (%)	54 (37.8)	5 (41.7)	10 (40.0)	30 (39.0)	4 (30.8)	5 (31.3)	0.781
Obese, n (%)	30 (21.0)	1 (8.3)	5 (20.0)	16 (20.8)	5 (38.5)	3 (18.8)	0.781

	All (n=143)	Lung or double lung (n=12)	Liver (n=25) ^a	Kidney (n=77)	Heart (n=13) ^a	Kid/panc or pancreas (n=16)	Between-group sig.
Current smoking, n (%)	7 (4.9)	2 (16.7)	2 (8.0)	2 (2.6)	0 (0)	1 (6.3)	0.119
Alcohol use > 1 per week, n (%)	20 (14.0)	1 (8.3)	2 (8.0)	16 (20.8)	0 (0)	1 (6.3)	0.140
Caffeine drink > 3 per day, n (%)	35 (24.5)	4 (33.3)	7 (28.0)	20 (26.0)	1 (7.7)	3 (18.8)	0.552
Lack of exercise, n (%)	21 (14.7)	1 (8.3)	3 (12.0)	10 (13.0)	1 (7.7)	6 (37.5)	0.097

^a Group includes one patient who also had a kidney transplant

* p < 0.05

** p < 0.01

*** p < 0.001.

Table 2

Self-reported sleep quality by transplant type (n=143)

	All (n=143)	Lung or double lung (n=12)	Liver (n=25) ^a	Kidney (n=77)	Heart (n=13) ^a	Kid/panc or pancreas (n=16)	Between-group sig.
PSQI, mean $\pm$ SD	7.9 $\pm$ 4.3	7.0 $\pm$ 5.3	8.3 $\pm$ 4.2	7.6 $\pm$ 4.2	8.6 $\pm$ 4.7	8.3 $\pm$ 4.8	0.828
PSQI > 8, n (%) ^b	58 (40.8)	3 (27.3)	12 (48.0)	32 (41.6)	5 (38.5)	6 (37.5)	0.829
PSQI > 5, n (%) ^b	92 (64.8)	6 (54.5)	18 (72.0)	46 (59.7)	9 (69.2)	13 (81.3)	0.413
Sleep latency (min), n (%)							
0-15	30 (21.6)	4 (33.3)	2 (8.3)	19 (25.3)	2 (15.4)	3 (20.0)	
> 15 and 30	60 (43.2)	5 (41.7)	14 (58.3)	31 (41.3)	6 (46.2)	4 (26.7)	0.213
> 30 and 60	24 (17.3)	1 (8.3)	3 (12.5)	15 (20.0)	0 (0)	5 (33.3)	
> 60	25 (18.0)	2 (16.7)	5 (20.8)	10 (13.3)	5 (38.5)	3 (20.0)	
Sleep duration (h), n (%)							
7	72 (50.7)	8 (72.7)	12 (48.0)	41 (53.2)	6 (46.2)	5 (31.3)	
6 and < 7	40 (28.2)	1 (9.1)	7 (28.0)	19 (24.7)	5 (38.5)	8 (50.0)	0.623
5 and < 6	16 (11.3)	1 (9.1)	3 (12.0)	10 (13.0)	0 (0)	2 (12.5)	
< 5	14 (9.9)	1 (9.1)	3 (12.0)	7 (9.1)	2 (15.4)	1 (6.3)	
Sleep efficiency (%), n (%)							
85	61 (43.0)	5 (45.5)	10 (40.0)	35 (45.5)	3 (23.1)	8 (50.0)	
75 and < 85	45 (31.7)	4 (36.4)	8 (32.0)	21 (27.3)	7 (53.8)	5 (31.3)	0.912
65 and < 75	15 (10.6)	1 (9.1)	2 (8.0)	9 (11.7)	1 (7.7)	2 (12.5)	
< 65	21 (14.8)	1 (9.1)	5 (20.0)	12 (15.6)	2 (15.4)	1 (6.3)	
Use of sleep medications, n (%)							
Not in last month	92 (64.3)	9 (75.0)	13 (52.0)	52 (67.5)	10 (76.9)	8 (50.0)	
< 1x/week	12 (8.4)	0 (0)	4 (16.0)	7 (9.1)	0 (0)	1 (6.3)	0.524
1 or 2x/week	12 (8.4)	2 (16.7)	2 (8.0)	6 (7.8)	0 (0)	2 (12.5)	
3x/week	27 (18.9)	1 (8.3)	6 (24.0)	12 (15.6)	3 (23.1)	5 (31.3)	
Sleep diagnosis or treatment, n (%)							
OSA	22 (15.4)	2 (16.7)	2 (8.0)	12 (15.6)	3 (23.1)	3 (18.8)	0.773
RLS	6 (4.2)	3 (25.0)	0 (0)	2 (2.6)	0 (0)	1 (6.3)	0.004**

*p < 0.05

***p < 0.001.

^aGroup includes one patient who also had a kidney transplant.^bOne patient did not report sleep duration and therefore did not get a PSQI total score at baseline.**
p < 0.01

Table 3

Risk factors for poor sleep defined as PSQI > 8 based on hierarchical multiple logistic regression models

Variables ^a	Model 1		Model 2 ^b	
	b (SE)	b ^c (95% CI)	b (SE)	b ^c (95% CI)
All patients (n=143)				
<i>Clinical factor</i>				
Use of medications for sleep, anxiety, or depression in last month	2.04 (0.41)***	7.69 (3.46-17.11)***	1.57 (0.50)**	4.82 (1.81-12.82)**
<i>Lifestyle factor</i>				
Employment (1 = Full or part time)	-0.99 (0.41)*	0.37 (0.17-0.83)*	-1.41 (0.52)**	0.24 (0.09-0.67)**
<i>Sentinel Symptom</i>				
Anxiety			0.07 (0.03)*	1.07 (1.01-1.14)*
Fatigue			0.06 (0.03)*	1.06 (1.00-1.13)*
Hosmer-Lemeshow statistics (p-value)	3.52 (0.47)		6.97 (0.54)	
-2 Log likelihood	149.62		113.87	
Pseudo-R ²	0.34		0.56	
Patients with kidney transplant (n=77)				
<i>Clinical factor</i>				
Use of medications for sleep, anxiety, or depression in last month	2.48 (0.59)***	11.93 (3.76-37.88)***	2.80 (0.86)**	16.51 (3.05-89.29)**
<i>Lifestyle factor</i>				
No exercise	1.93 (0.96)*	6.91 (1.06-45.19)*	-	-
<i>Sentinel Symptom</i>				
Fatigue			0.16 (0.06)*	1.17 (1.04-1.33)*
Hosmer-Lemeshow statistics (p-value)	2.51 (0.64)		3.67 (0.89)	
-2 Log likelihood	74.15		46.18	
Pseudo-R ²	0.42		0.71	

^aThe demographic and clinical factors shown in Table 1, sleep diagnosis factors (OSA, RLS), and treatment type were screened for associations with poor sleep defined by PSQI (p < 0.10) prior to inclusion in these multivariate models.

b Sentinel symptoms were included in Model 2.
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$.

Table 4

Sleep parameters based on actigraphy by transplant type (n=73)

	All (n=73)	Lung or double lung (n=6)	Liver (n=15) ^a	Kidney (n= 32)	Heart (n=11) ^a	Kid/panc or pancreas (n=9)	Between-group sig. ^b
Total sleep time (TST) in hours, mean (range)	6.7 (4.8-9.2)	6.9 (5.1-8.7)	6.9 (5.3-8.8)	6.8 (4.9-9.2)	6.4 (5.3-8.2)	6.1 (4.8-7.3)	.192
TST < 6 hours (%)	24.7%	33.3%	20.0%	12.5%	45.5%	44.4%	.115
Sleep onset latency (SOL) in minutes, mean (range)	28.2 (1.3 - 114.1)	28.3 (12.8-48.6)	44.4 (8.6-114.1)	21.3 (1.3-62.8)	28.0 (8.5-45.1)	26.4 (9.4-49.9)	.014
SOL > 30 minutes (%)	31.5%	33.3%	40.0%	25.0%	36.4%	33.3%	.866
Wake after sleep onset (WASO) in minutes, mean (range)	56.2 (12.0-249.3)	48.5 (16.7-77.6)	61.5 (23.0-119.6)	51.1 (12.0-91.2)	72.3 (28.6-249.3)	51.2 (22.4-82.0)	.319
WASO > 30 minutes (%)	87.7%	83.3%	80.0%	90.6%	90.9%	88.9%	.862
Sleep efficiency (SE) %, mean (range)	80.1 (56.7 - 95.9)	80.9 (68.9-89.8)	77.6 (59.7-88.3)	82.0 (69.2-95.9)	77.2 (56.7-88.0)	80.1 (66.7-87.0)	.267
SE < 85% (%)	68.5%	50.0%	73.3%	65.6%	81.8%	66.7%	.707

^a Group includes one patient who also had a kidney transplant.

^b ANOVAs for continuous data, Chi-square tests for proportions in categories of poor sleep.

Table 5

Risk factors for poor sleep defined by actigraphy (n=73)

Indicator for poor sleep	Variable ^a	Final model	
		b (SE)	e ^b (95% CI)
SOL > 30 min	<i>Clinical factor</i>		
	Use of medications for depression, anxiety, or sleep in last month	2.06 (0.73) **	7.81 (1.86-32.82) **
	<i>Lifestyle factor</i>		
	Obesity	1.68 (0.76) *	5.39 (1.22-23.78) *
	Hosmer-Lemeshow statistics (p value)		10.72 (0.22)
	-2 Log likelihood		66.14
TST < 6 hr	Pseudo-R ²		0.40
	<i>Clinical factor</i>		
	Treatment type (1 = kidney treatment only)	-2.10 (0.81) **	0.12 (0.03-0.60) **
	<i>Lifestyle factor</i>		
	Obesity	2.10 (0.81) **	8.20 (1.69-39.92) **
	<i>Sentinel Symptom</i>		
SE < 85%	Pain	0.11 (0.04) *	1.11 (1.02-1.21) *
	Hosmer-Lemeshow statistics (p value)		20.56 (0.01)
	-2 Log likelihood		63.11
	Pseudo-R ²		0.33
	<i>Lifestyle factor</i>		
	Employment (1 = Full or part time)	-1.82 (0.66) **	0.16 (0.04-0.59) **
SE < 85%	Obesity	1.77 (0.89) *	5.86 (1.03-33.47) *
	Hosmer-Lemeshow statistics (p value)		12.26 (0.14)
	-2 Log likelihood		71.30
	Pseudo-R ²		0.32

***p < 0.001

^aThe demographic and clinical factors shown in Table 1, sleep diagnosis factors (OSA, RLS), and treatment type were screened for associations with poor sleep defined by SOL, TST, and SE (p < 0.10) prior to inclusion in these multivariate models.

*
p < 0.05

**
p < 0.01