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Disturbed sleep after lung transplantation is associated with worse patient-reported outcomes and chronic lung allograft dysfunction

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BACKGROUND: Many lung transplant recipients fail to derive the expected improvements in health-related quality of life (HRQL) and survival. Sleep may represent an important, albeit rarely examined, factor associated with lung transplant outcomes.

METHODS: Within a larger cohort study, 141 lung transplant recipients completed the Medical Outcomes Study Sleep Problems Index (SPI) Revised scale along with a broader survey of patient-reported outcome (PRO) measures and frailty assessment. From the SPI, we also derived an insomnia-specific subscale. Potential perioperative risk factors for disturbed sleep were derived from medical records. We investigated associations between perioperative predictors on SPI and insomnia and associations between SPI and insomnia on PROs and frailty by linear regressions, adjusting for age, sex, and lung function. We evaluated the associations between SPI and insomnia on time to chronic lung allograft dysfunction (CLAD) and death using Cox models, adjusting for age, sex, and transplant indication.

RESULTS: Post-transplant hospital length of stay > 30 days was associated with worse sleep by SPI and insomnia (SPI: $p = 0.01$; insomnia $p = 0.02$). Worse sleep by SPI and insomnia was associated with worse depression, cognitive function, HRQL, physical disability, health utilities, and Fried Frailty Phenotype frailty (all $p < 0.01$). Those in the worst quartile of SPI and insomnia exhibited an increased risk of CLAD (hazard ratio [HR] 2.18; 95% confidence interval [CI]: 1.22-3.89; $p = 0.01$ for SPI and HR 1.96; 95%CI 1.09-3.53; $p = 0.03$ for insomnia). Worsening in SPI but not insomnia was also associated with mortality (HR: 1.29; 95%CI: 1.05-1.58; $p = 0.01$).

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CONCLUSIONS: Poor sleep after lung transplant appears associated with PROs, frailty, CLAD, and death. Clarifying the nature of this association may have important screening implications.
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Background

Lung transplantation aims to extend survival, relieve disability, and improve health-related quality of life (HRQL).[1] Although many do well, perioperative complications are increasing, 20% to 30% of survivors do not report substantive improvements in physical functioning or HRQL, and 1 in 3 die within the first 3 postoperative years.[2-8] In response to these frequent and increasing barriers to transplant success, identifying modifiable factors that could support transplant recovery and improve HRQL is needed. Sleep may be one potential behavioral pathway, although its impacts on outcomes after lung transplantation are not well characterized.

Sleep plays a fundamental role in physical health, well-being, and recovery from illness. The potential for sleep disturbances after lung transplant is high, particularly during the dynamic perioperative and early postoperative period that is increasingly complicated by primary graft dysfunction (PGD; a form of acute post-transplant lung injury), delirium, prolonged hospital stays, post-traumatic stress, readmissions, and intense immunosuppression.[5,9-13] Disturbed sleep has the potential to significantly impair transplant success. Outside of the lung transplant context, disturbed sleep is associated with impaired cognition, mood dysregulation (particularly depression), risk of frailty, and immune dysfunction.[14-22] In addition to being important outcomes to lung transplant recipients themselves, depression, frailty, and immune dysfunction have previously been shown to also predict disability, chronic lung allograft dysfunction (CLAD), and mortality after transplant.[23-27]

To date, a relatively limited number of studies have examined sleep after lung transplantation and even fewer have examined the impact of disturbed sleep on post-transplant outcomes.[28] Depending on the sleep measure used, between 30% and 74% of lung transplant recipients reported disturbed sleep; when present, disturbed sleep was associated with depression and anxiety.[28]

To address these gaps, in this single-center cohort study, we sought to examine potential perioperative predictors of disturbed sleep after lung transplant and whether disturbed sleep is associated with disability, HRQL, and frailty. We additionally sought to test whether disturbed sleep was associated with risk of CLAD onset and mortality.

Methods

Study design

We performed this study among a subset of participants of the University of California San Francisco (UCSF) "Breathe Again" cohort. "Breathe Again" is a single-center, longitudinal, repeated measure prospective cohort study of 392 lung transplant candidates, 259 of whom underwent first-time lung transplantation between 2010 and 2017.[29] Briefly, Breathe Again participants completed study visits that included a survey of patient-reported outcomes (PROs) as well as measures of physical frailty before and repeatedly after lung transplantation. Between November 2013 and August 2016, we asked a random sample subset of Breathe Again participants to complete a supplemental pilot PRO survey battery that included the Medical Outcomes Study (MOS) Sleep Problems Index Revised I Scale.[30] This pilot survey was administered once to these randomly selected Breathe Again study participants (n = 141) during regularly scheduled study visits. This pilot survey ultimately yielded the Lung Transplant Quality of Life (LTQOL) measure.[31] Details of the pilot survey composition and administration are detailed in reporting of LTQOL development.[31] It is this group of 141 that forms the group analyzed herein. All patients signed informed consent and our study was approved by the UCSF Institutional Review Board. Of note, given the primary focus of the Breathe Again study, our consent form did not include permission to access prescription filling records from local pharmacies.

Clinical practice

Clinically, systematic formal screening for sleep problems, assessments of adherence to sleep aids such as continuous positive airway pressure (CPAP)/bilevel positive airway pressure (BiPAP), and cognitive functioning are not routinely performed. Similarly, after transplant, recommendations for polysomnography are based on clinical suspicion of sleep-disordered breathing. Efforts to address clinical reports of difficulty sleeping after transplant largely involve pharmacologic interventions, reassurance that sleep may improve with lower doses of prednisone, and general recommendations to promote sleep hygiene. Due to the large geographic spread of the UCSF lung transplant recipient population, the clinical program generally needs to engage patients' local providers to perform polysomnography if sleep-disordered breathing is suspected. Access to local testing facilities and results is inconsistent.

Measures of sleep

We evaluated sleep by the 6 items used to calculate the Sleep Problems Index (SPI) summary scale from the Medical Outcomes Study Sleep Scale-Revised (MOS-Sleep) scale. The

MOS-Sleep is a 12-item measure that contains 7 subscales and 2 overall index scores (a 6- and 9-item SPI).[30] Respondents answered how often over the prior 4 weeks they experienced various sleep problems, such as getting enough sleep to feel rested or having trouble falling asleep. These items are detailed in Appendix Table 1. To further understand the specific impact of insomnia, we also explored an insomnia-specific subscale based on the face validity of 2 of the 6 MOS-Sleep items. These insomnia-focused items query how often respondents had trouble falling asleep and how often respondents awakened during sleep time and then had trouble falling asleep again.

Predictor variables of interest

Based on sleep literature from other medical and surgical patient populations, we considered several demographic and perioperative factors as potential risk factors for disturbed sleep after transplant. Preoperative factors considered included age, sex, transplant indication, body mass index, and pretransplant depressive symptoms. Perioperative factors considered included location at the time of donor offer (home vs hospitalized) as well as postoperative intensive care unit (ICU) delirium, severe PGD, ICU length of stay (LOS), and postoperative prolonged overall hospital LOS. ICU delirium was defined as ever being delirious in the ICU after lung transplant surgery by medical record review of nursing-administered Confusion Assessment Method for the ICU[32] screens once per shift. Severe PGD was defined as grade 3 PGD on postoperative day 2 or 3 per International Society of Heart and Lung Transplantation consensus.[33] Prolonged overall hospital LOS was defined as post-transplant LOS lasting 30 or more days after transplant.[5]

Outcome variables of interest

All participants in *Breathe Again* completed a complex study battery of patient-reported battery (PROs) and frailty before and repeatedly up to 36 months after transplant. For this analysis, we selected the survey responses and frailty assessments after transplant that were collected concurrent with the pilot survey.

Patient-reported outcomes

The survey measures included instruments to assess functioning/disability, depressive symptoms, generic and respiratory-specific HRQL, and health utilities. In addition to the Sleep Scale, the pilot survey also included the original MOS Cognitive Functioning Scale[30] that has been rescaled and adapted to become the Lung Transplant Quality of Life Cognitive Limitations subscale (LTQOL-Cog).[31] Functioning/disability was assessed by the Lung Transplant Valued Life Activities Scale (LT-VLA; 15 items; range 0-3; minimally important difference [MID]: 0.3; higher scores denote worse disability). Depressive symptoms were quantified by the Geriatrics Depression Scale-15 (GDS; 15 items; range 0-15; MID: 1.65; higher scores denote worse depressive symptoms). Generic HRQL was evaluated by the RAND Medical Outcomes Study Short Form 36 Physical and Mental Composite Summary scales (SF36PCS and MCS; 36 items; range 0-100; MID 5; lower scores denote worse HRQL). Respiratory-specific HRQL was assessed with the Airways Questionnaire 20-Revised (AQ20R; 20 items; range 0-20; MID 1.75; higher scores denote worse HRQL). Health utility was assessed by the EuroQol 5D (EQ5D; 5 items; range −0.11 to 1.0; MID 0.06; higher scores denote better health utility). Finally, self-reported cognitive functioning was assessed by the LTQOL-Cog (6 items; range 1-5; MID: 0.47; higher scores denote worse cognitive functioning).

Frailty

We assessed frailty by 2 well-validated frailty measures that emphasize physical functioning. The Short Physical Performance Battery (SPPB) is a 3-component battery of lower extremity performance measures that include gait speed, chair stands, and balance.[34,35] Each measure is scored from 0 to 4 with an aggregate score ranging from 0 to 12. Lower SPPB scores reflect increased frailty. The Fried Frailty Phenotype (FFP) is an aggregate score of 5 constructs: shrinking, exhaustion, low physical activity, slowness, and weakness.[36] The FFP ranges from 0 to 5 with higher scores reflecting increased frailty.

Chronic lung allograft dysfunction

CLAD was defined as 20% decline in forced expiratory volume in 1 sec (FEV1) from post-transplant baseline that persisted for at least 3 months.[37] All pulmonary lung functions after transplant were abstracted from medical records. Time to CLAD was calculated as the number of days from the date of lung transplantation until the first sustained 20% drop in FEV1.

Mortality

Dates of death were obtained through the Social Security Master Death File. Survival time was calculated as the number of days from the date of lung transplantation until the date of death.

Other measurements

Demographic and clinical variables were abstracted from medical records. Variables included age, sex, race/ethnicity, diagnostic indication for transplant, transplant type (single vs bilateral vs heart-lung), and all measures of lung function (FEV1; liters and forced vital capacity [FVC; liters]) after transplant.

Analytic approach

We used the overall SPI and 2 insomnia-focused items to test the association between both disturbed sleep and

insomnia on our outcomes of interest. The SPI and the insomnia subscale do not have established thresholds to define disturbed sleep or insomnia. Conceptually, *any* impairment in sleep could plausibly be associated with how people feel and function. Therefore, we analyzed the SPI and insomnia subscale on a continuous scale (per MID worsening) and as binary variables comparing the worst quartile to the rest. Some scales, such as the SF36 and EQ5D, have established anchor-based MIDs. For many PROs, including the MOS-Sleep, anchor-based MIDs are not available. In these cases, distribution-based methods are employed with one-half the observed standard deviation (SD) being the most common.[38] For this analysis, we defined SPI and insomnia MIDs by one-half the observed SD, as we have done previously.[29]

To investigate the associations between preoperative and perioperative variables on SPI and insomnia as continuous and as binary outcomes, we used linear and logistic regression, respectively, adjusting for age, sex, preoperative lung function, and preoperative CPAP/BiPAP therapy. To investigate the association between SPI and insomnia as continuous and binary exposure variables on PROs and frailty, we used linear regression, adjusting for age, sex, transplant indication, and postoperative lung function. We fit Cox proportional hazards models to evaluate the associations between SPI and insomnia with time to CLAD and time to death adjusted for age, sex, and transplant indication. The proportional hazards assumption was tested using Schoenfeld residuals. We used Kaplan-Meier methods to visualize the relationship association between the SPI and insomnia defined categorically with CLAD and death. We used the Survival Area Plot method to visualize the unadjusted association between the SPI and insomnia as continuous variables with CLAD and death.[39] Of those who completed the pilot survey that included MOS-Sleep, all respondents completed all sleep survey items. Rarely (< 2%) missing specific survey items other than MOS-Sleep was handled as previously detailed[29]; there were no missing demographic, perioperative, CLAD, or mortality data, nor loss to follow-up.

Given that our original cohort was not designed, a priori, to study the association between sleep and outcomes after transplant, we conducted a series of exploratory analyses. First, if poorer patient-reported sleep was associated with outcomes after transplant, we considered that poor sleep might be a marker of other factors such as more complicated perioperative courses (e.g., PGD, prolonged LOS). Thus, in 1 exploratory analysis, we planned to control for perioperative predictors identified as being associated with poor sleep in analyses evaluating the association between SPI and insomnia with time to CLAD and time to death. A priori, however, we also recognized that this modeling could also represent a mediation analysis in which poor sleep lies on the association pathway between perioperative complications and outcomes after transplant. Next, we recognized that our surveys were completed across a relatively broad postoperative time frame. It is possible that sleep problems improve as time from transplant lengthens and/or that the potential association between poor sleep and outcomes after transplant differs depending on time since transplant. Thus, as another set of exploratory analyses, we repeated our primary analyses stratifying our cohort by median time after transplant of survey completion.

Finally, not all participants approached completed the pilot survey. From the primary Breathe Again study, reasons for noncompletion were recorded in real time. Surveys were deemed missing at random if subjects did not complete surveys for reasons other than their health and were not hospitalized nor dealing with acute medical issues and had stable allograft function. Surveys were deemed missing not at random if subjects were too ill to complete the survey.

Analyses were performed using SAS (version 9.4, SAS Institute), and R (version 4.3.1, R Foundation).

Results

During the Breathe Again study period, of 164 lung transplant recipients approached, 141 completed the pilot survey that included MOS-Sleep and formed our study cohort (86% response rate). These 141 participants were 43% female with a mean age of 58 years (SD ± 13); 75% were non-Hispanic White and 5 (3.5)% were prescribed CPAP or BiPAP before transplant (Table 1). Most participants underwent transplant for pulmonary fibrosis (72%) followed by nonsuppurative obstructive lung diseases (15%). Participants completed the study battery used in these analyses at a median of 1.5 years after transplant (interquartile range: 0.6, 2.4). Over the study period, 52 (37%) developed CLAD and 20 (14%) died. Participants in this sleep survey pilot were representative of the overall Breathe Again study cohort who were 45% female, 68% non-Hispanic White, and 68% of whom underwent transplant for pulmonary fibrosis.[40]

Of the predictors tested, preoperative depressive symptoms, ICU LOS, and post-transplant hospital LOS lasting ≥30 days were all generally associated with disturbed sleep and insomnia, after adjusting for age, sex, and lung function (Table 2). For example, worsening in preoperative depressive symptoms by the MID was associated with 1.8 points worse adjusted SPI scores (1.76; 95% confidence interval [CI]: 0.41, 3.12; $p = 0.01$) and 2.9 points worse adjusted insomnia scores (2.88; 95%CI: 0.94, 4.82; $p < 0.01$). Prolonged LOS was associated with an 8.5-fold higher odds of being in the worst quartile of SPI disturbed sleep (adjusted odds ratio [aOR] 8.5; 95%CI: 2.33, 31.03; $p < 0.01$). Prolonged ICU and overall LOS, however, were not significantly associated with being in the worst quartile of insomnia (aOR: 1.79; 95%CI: 0.72, 4.45; $p = 0.21$ and aOR: 1.70; 95%CI: 0.47, 6.09; $p = 0.42$, respectively). Neither being in the hospital at the time of donor offer, PGD, nor delirium were significantly associated with disturbed sleep or insomnia (all $p > 0.05$) (Table 2). Notably, preoperative depressive symptoms were not associated with risk of CLAD nor death after transplant ($p = 0.56$ and $p = 0.91$, respectively).

We also found consistent associations between disturbed sleep, either as a continuous variable or dichotomized as worst vs the top 3 quartiles, and all PROs of interest, after

Table 1 Participant Characteristics

No. of subjects	N = 141
Woman, No. (%)	60 (42.6)
Age, mean ± SD	57.6 ± 12.7
Age, range	21.5 - 74.3
Race/ethnicity, No. (%)	
White, non-Hispanic	105 (74.5)
White, Hispanic	17 (12.1)
Black	10 (7.1)
Asian	8 (5.7)
American Indian	1 (0.7)
Diagnostic indication for transplant, No. (%)	
Group A (e.g., obstructive lung disease)	21 (14.9)
Group B (e.g., pulmonary hypertension)	5 (3.6)
Group C (e.g., suppurative lung disease)	13 (9.2)
Group D (e.g., pulmonary fibrosis)	102 (72.3)
BMI (kg/m^2), mean ± SD	25.1 ± 4.5
Preoperative GDS depressive symptoms score, median [IQR]	5 [3, 8]
FEV1 (liter) mean (SD)	2.5 ± 0.9
FEV1% predicted, mean (SD)	80.5 ± 24.2
FVC (liter) mean (SD)	3.1 ± 1.0
FVC % predicted, mean (SD)	77.1 ± 20.1
On BiPAP or CPAP before transplant, *n* (%)	5 (3.5)
Inpatient at the time of donor offer *n* (%)	35 (25)
Severe primary graft dysfunction after transplant, *n* (%)	31 (22.0
ICU delirium after transplant, *n* (%)	15 (15.3)
ICU length of stay (days), median [IQR]	6 [5, 9]
Overall length of stay in hospital (days), median [IQR]	16 [13, 21]
Deaths within 5 years after transplant, *n* (%)	20 (14.2)
CLAD* within 5 years after transplant, *n* (%)	52 (36.9)
Transplant type, No. (%)	
Bilateral	129 (91.5)
Single	11 (7.8)
Heart/lung	1 (0.7)
Time post-transplant when survey was completed, median [IQR] (years)	1.5 [0.6, 2.4]
Time point post-transplant when survey was completed, range (years)	0.2-4.1
≥0 and ≤1	57
> 1 and ≤2	43
> 2 and ≤3	23
> 3	18

Abbreviations: BMI, body mass index; BiPAP, bilevel positive airway pressure; CLAD, chronic lung allograft dysfunction; CPAP, continuous positive airway pressure; FEV1, forced expiratory volume in 1 sec; FVC forced vital capacity; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

Data are presented as number of patients (percentage) or mean ± standard deviation.

adjusting for age, sex, transplant indication, and allograft function (Table 3). For example, for each MID worsening in the SPI participants reported worse depressive symptoms (GDS: 0.63; 95%CI: 0.32, 0.94; $p < 0.01$; MID = 1.65), generic mental HRQL (SF36MCS: −2.04; 95%CI: −2.75, −1.33; $p < 0.01$; MID = 5), and health utilities (EQ5D: −0.03; 95%CI: −0.04, −0.02; $p < 0.01$; MID = 0.06). Similarly, participants in worst quartile of SPI reported substantially worse respiratory-specific HRQL (AQ20R: 3.53; 95%CI: 1.79, 5.26; $p < 0.01$; MID = 1.75), cognitive functioning (LTQOL-Cog: 0.63; 95%CI: 0.31, 0.96; $p < 0.01$; MID = 0.47), and generic physical HRQL (SF36PCS: −6.99; 95%CI: −10.67, −3.30; $p < 0.01$; MID = 5). Insomnia symptoms were similarly strongly associated with our PROs of interest after adjusting for prespecified confounders (Table 4).

Poorer sleep and insomnia symptoms were also generally associated with worse physical functioning and frailty by FFP (Tables 3 and 4). For example, each MID worsening in SPI was associated with disability (LT-VLA: 0.05; 95%CI: 0.02, 0.09; $p < 0.01$; MID = 0.3) and frailty (FFP: 0.13; 95%CI: 0.04, 0.21; $p < 0.01$). Each MID worsening in insomnia was also associated with disability (LT-VLA: 0.05; 95%CI: 0.02, 0.09; $p < 0.01$; MID = 0.3) and frailty (FFP: 0.12; 95%CI: 0.03, 0.21; $p < 0.01$). Sleep did not appear to be significantly associated with frailty by SPPB.

Poorer sleep and insomnia also appeared to be associated with the development of CLAD and death after lung transplantation. For example, adjusting for age, sex, and transplant indication, each MID worsening in sleep by SPI was associated with a 1.14-fold increased risk of CLAD (hazard ratio [HR] 1.14; 95%CI: 1.00, 1.30; $p = 0.04$) and a 1.29-fold increased risk of death (HR: 1.29; 95%CI: 1.05, 1.58; $p = 0.01$). The direction and magnitude of the associations were relatively consistent across analyses, although the strength of associations between binary SPI and insomnia with death after transplant did not reach statistical significance in tests. Results are detailed in Table 5 and in Figures 1 and 2.

Finally, we conducted a series of sensitivity analyses evaluating the association between disturbed sleep and our post-transplant outcomes of interest further controlling for postoperative LOS as a composite measure of a more challenging perioperative course. Across our evaluated PRO, CLAD, and mortality outcomes, our findings were essentially unchanged. For example, the association between the worst quartile of poor sleep and depressive symptoms without controlling for LOS was 2.35 (95%CI: 0.97, 3.73) points compared with 2.37 (0.91, 3.82) (MID for depressive symptoms: 1.65). Similarly, the HR of the worst quartile of poor sleep and time to CLAD without controlling for LOS was 2.18 (95%CI: 1.22, 3.89) compared with 2.18 (95%CI: 1.17, 4.06). Appendix Tables 2 to 4 detail the rest of the analyses controlling for postoperative hospital LOS.

Discussion

In this single-center study, we found that preoperative depressive symptoms and prolonged postoperative and ICU and hospital stays were associated with disturbed sleep and insomnia which, in turn, were associated with worse cognitive functioning, depressive symptoms, and poorer HRQL. Disturbed sleep and insomnia were also associated with disability and frailty as well as increased risk of CLAD

Table 2 Pre and Peri-Operative Risk Factors for Disturbed Sleep and Insomnia After Transplant

	Continuous scale		Worst quartile	
Predictor	Parameter estimate (95%CI)	*p*-value	Odds ratio (95%CI)	*p*-value
	Sleep Problem Index (SPI) SPI MID = 8			
Preoperative depressive symptoms	1.79 (0.42, 3.15)	0.01	1.05 (0.86, 1.28)	0.61
Hospitalized at the time of donor offer	−0.51 (−7.22, 6.19)	0.88	1.37 (0.56, 3.38)	0.49
Severe PGD	4.08 (−2.43, 10.6)	0.22	0.97 (0.39, 2.45)	0.95
ICU length of stay (per 1 day)	0.41 (0.14, 0.69)	< 0.01	1.05 (1.01, 1.09)	0.02
Length of hospital stay > 30 days	12.55 (3.70, 21.41)	0.01	7.09 (2.10, 23.95)	< 0.01
Delirium	0.40 (−9.06, 9.86)	0.93	2.40 (0.69, 8.38)	0.17
	Insomnia Insomnia MID = 12			
Preoperative depressive symptoms	2.87 (0.91, 4.83)	< 0.01	1.30 (1.06, 1.58)	0.01
Hospitalized at the time of donor offer	1.68 (−7.76, 11.13)	0.72	0.76 (0.28, 2.02)	0.58
Severe PGD	1.62 (−7.60, 10.85)	0.73	0.72 (0.27, 1.92)	0.51
Length of hospital stay > 30 days	14.80 (2.23, 27.38)	0.02	1.69 (0.47, 6.04)	0.42
ICU length of stay (per 1 day)	0.69 (0.30, 1.08)	< 0.01	1.02 (0.99, 1.06)	0.20
Delirium	2.77 (−10.29, 15.83)	0.67	0.67 (0.13, 3.40)	0.63

Abbreviations: CI, confidence interval; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FEV1, forced expiratory volume in 1 sec; ICU, intensive care unit; MID, minimally important difference; PGD, primary graft dysfunction.

Models adjusted for age, sex, preoperative FEV1, and preoperative use of BiPAP or CPAP.

Table 3 Association Between Sleep Problem Index With Patient-Centered Outcomes

		Parameter estimate[a]	
Outcome variable (MID)	Conceptual domain measured	SPI MID = 8	*p*-value
LT-VLA	Physical functioning/disability	Per MID worsening: 0.05 (0.02, 0.09)	< 0.01
MID = 0.3		Worst quartile: 0.16 (−0.01, 0.32)	0.06
GDS	Depression	Per MID worsening: 0.63 (0.32, 0.94)	< 0.01
MID = 1.65		Worst quartile: 2.35 (0.97, 3.73)	< 0.01
Cognitive limitations	Cognitive impairments	Per MID worsening: 0.17 (0.10, 0.24)	< 0.01
MID = 0.47		Worst quartile: 0.63 (0.31, 0.96)	< 0.01
SF36PCS	Generic physical HRQL	Per MID worsening: 1.93 (−2.7, −1.15)	< 0.01
MID = 5		Worst quartile: −6.99 (−10.67, −3.30)	< 0.01
SF36MCS	Generic mental HRQL	Per MID worsening: −2.04 (−2.75, −1.33)	< 0.01
MID = 5		Worst quartile: −8.64 (−11.96, −5.31)	< 0.01
AQ20R	Respiratory-specific	Per MID worsening: 0.91 (0.52, 1.30)	< 0.01
MID = 1.75		Worst quartile: 3.53 (1.79, 5.26)	< 0.01
EQ5D	Health utility	Per MID worsening: −0.03 (−0.04, −0.02)	< 0.01
MID = 0.06		Worst quartile: −0.11 (−0.17, −0.05)	< 0.01
SPPB	Physical frailty	Per MID worsening: −0.07 (−0.22, 0.08)	0.34
MID = 1		Worst quartile: 0.09 (−0.60, 0.79)	0.79
FFP	Physical frailty	Per MID worsening: 0.13 (0.04, 0.21)	< 0.01
MID = 1		Worst quartile: 0.52 (0.14, 0.90)	0.01

Abbreviations: AQ20R, Airways Questionnaire 20-Revised; EQ5D, EuroQoL 5 Dimensions (5-level version); FEV1, forced expiratory volume in 1 sec; FFP, Fried Frailty Phenotype; GDS, Geriatric Depression Scale; LT-VLA, Lung Transplant Valued Life Activities scale; MID, minimally important difference; SF36MCS, Short Form 36 Mental Component Summary Scales; SF36PCS, Short Form 36 Physical Component Summary Scales; SPI, Sleep Problems Index; SPPB, Short Physical Performance Battery.

[a]Adjusted for age, sex, transplant indication, and FEV1.

and mortality. Notably, preoperative depression was not associated with postoperative CLAD or death and controlling for prolonged length of transplant surgery hospital stay—a composite marker of complicated postoperative courses—did not change our observed associations. These findings suggest that poorer sleep after transplant was not simply a marker of depressive symptoms or perioperative complications.

Our findings raise the possibility that sleep may play an important role in physical and mental health outcomes in lung transplantation, as it does in other populations. They also add important insights into the relatively little that is currently

Table 4 Association Between Insomnia and Patient-Centered Outcomes

Outcome variable (MID)	Conceptual domain measured	Parameter estimate[a] Insomnia subscale MID = 12	*p*-value
LT-VLA	Physical functioning/disability	Per MID worsening: 0.05 (0.02, 0.09)	< 0.01
MID = 0.3		Worst quartile: 0.22 (0.06, 0.38)	0.01
GDS	Depression	Per MID worsening: 0.58 (0.25, 0.90)	< 0.01
MID = 1.65		Worst quartile: 2.33 (0.96, 3.70)	< 0.01
Cognitive limitations	Cognitive impairments	Per MID worsening: 0.18 (0.11, 0.25)	< 0.01
MID = 0.47		Worst quartile: 0.71 (0.39, 1.03)	< 0.01
SF36PCS	Generic physical HRQL	Per MID worsening: −1.76 (−2.59, −0.93)	< 0.01
MID = 5		Worst quartile: −6.57 (−10.28, −2.86)	< 0.01
SF36MCS	Generic mental HRQL	Per MID worsening: −1.98 (−2.74, −1.22)	< 0.01
MID = 5		Worst quartile: −8.26 (−11.62, −4.90)	< 0.01
AQ20R	Respiratory-specific	Per MID worsening: 1.06 (0.67, 1.44)	< 0.01
MID = 1.75		Worst quartile: 4.47 (2.87, 6.07)	< 0.01
EQ5D	Health utility	Per MID worsening: −0.02 (−0.04, −0.01)	< 0.01
MID = 0.06		Worst quartile: −0.08 (−0.14, −0.02)	< 0.01
SPPB	Physical frailty	Per MID worsening: −0.05 (−0.21, 0.11)	0.54
MID = 1		Worst quartile: 0.13 (−0.57, 0.82)	0.72
FFP	Physical frailty	Per MID worsening: 0.12 (0.03, 0.21)	< 0.01
MID = 1		Worst quartile: 0.43 (0.03, 0.82)	0.03

Abbreviations: AQ20R, Airways Questionnaire 20-Revised; EQ5D, EuroQoL 5 Dimensions (5-level version); FEV1, forced expiratory volume in 1 sec; FFP, Fried Frailty Phenotype; GDS, Geriatric Depression Scale; HRQL, health-related quality of life; LT-VLA, Lung Transplant Valued Life Activities scale; MID, minimally important difference; SF36MCS, Short Form 36 Mental Component Summary Scales; SF36PCS, Short Form 36 Physical Component Summary Scales; SPPB, Short Physical Performance Battery.

[a]Adjusted for age, sex, transplant indication, and FEV1.

Table 5 Association Between Sleep Problem Index and Insomnia Subscale With CLAD and Death Adjusting for Age, Sex, and Transplant Indication

Sleep survey category	Exposure type	Time to CLAD Hazard ratio	Time to death Hazard ratio
Sleep Problem Index (SPI)	Per MID worsening	1.14 (1.00, 1.30)	1.29 (1.05, 1.58)
SPI MID = 8		*p* = 0.04	*p* = 0.01
	Worst quartile	2.18 (1.22, 3.89)	2.12 (0.84, 5.35)
		p = 0.01	*p* = 0.11
Insomnia	Per MID worsening	1.21 (1.05, 1.39)	1.16 (0.93, 1.44)
Insomnia MID = 12		*p* = 0.01	*p* = 0.20
	Worst quartile	1.96 (1.09, 3.53)	0.68 (0.22, 2.10)
		p = 0.03	*p* = 0.51

Abbreviations: CLAD, chronic lung allograft dysfunction; MID, minimally important difference.

known about the impact sleep has on PROs after lung transplantation. Among a small number of modest-sized studies, poorer sleep after lung transplant has been associated with worse depressive symptoms and poorer scores on the general mental health component of the SF36.[41-44] An understanding of poor sleep on other outcomes, however, remains largely unknown. Outside of lung transplantation, poorer sleep is associated with cognitive dysfunction and risk of frailty.[16,18,45-47] For example, experimental and epidemiologic data support links between poor sleep and impaired cognition, including difficulties in executive functioning, memory, and attention processes.[17] Notably, cognitive dysfunction following major cardiothoracic surgery is common and, in lung transplant, is associated with increased risk of mortality.[26,48-50] Sleep disturbance during this important recovery period may contribute to future cognitive outcomes. Further, a pooled analysis supports short and excessively long sleep duration, as well as a longer sleep onset latency as risk factors for frailty.[18]

Our study has several strengths. First, it is one of the largest studies of sleep and PROs in lung transplant. A recent scoping literature review of sleep quality following transplant identified just 9 research studies with sample sizes ranging from 20 to 219 participants. Our study is the second largest to date and links measures of sleep quality to outcomes beyond mental health. We newly identified associations between sleep and physical disability, frailty, CLAD, and even death after lung transplant. These findings, if confirmed in prospectively designed studies, raise the possibility that sleep disturbance may be an important and modifiable behavioral pathway to improve quality of life and clinical outcomes among lung transplant recipients.

Despite these strengths, it is important to emphasize that our study design precludes causal inference testing or

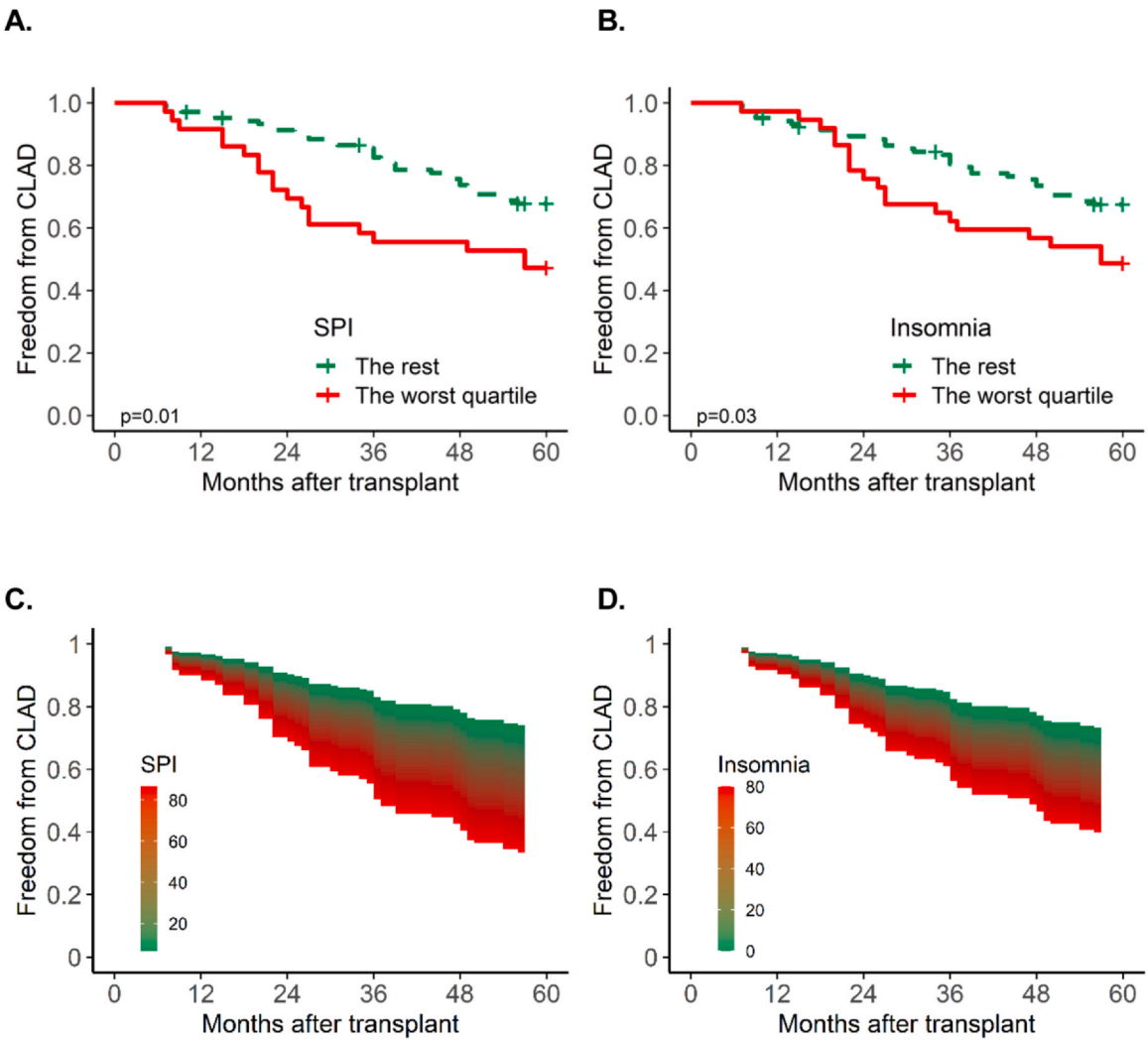

Figure 1 Kaplan-Meier estimate of the association of disturbed sleep by MOS-Sleep Problems Index (A) and insomnia-specific subscale (B) defined as categorical variables on time to CLAD. Survival area plot illustrating the association of disturbed sleep by MOS-Sleep Problems Index (C) and insomnia-specific subscale (D) defined as continuous variables on time to CLAD. CLAD, chronic lung allograft dysfunction; MOS, Medical Outcomes Study; SPI, Sleep Problems Index.

understanding mechanisms of association. For example, our measures of sleep were collected concurrent to other PROs. Thus, it remains unclear whether disturbed sleep caused depressive symptoms, poorer HRQL, and other PROs or whether the reverse may be true. Understanding the directionality of these relationships is key to further efforts including designing interventions aimed at improving patient-centered outcomes. It is also possible that unmeasured factors such as postoperative pain or dyspnea could have confounded our observations between disturbed sleep and PROs. Further, while the associations between disturbed sleep and cognitive, psychological, and HRQL outcomes may be more direct, the associations with physical impairments, including frailty and CLAD, may be less so. Behaviorally-driven factors such as impaired motivation to exercise regularly and to consume a balanced diet could drive disability and frailty whereas depression and cognitive impairment could impact medication adherence, thereby increasing risk of CLAD. It is also plausible that sleep's essential role in immune system dysregulation from disturbed sleep via enhanced systemic inflammation[20,51] and accelerated biological aging[19,52] *could* identify biological links between sleep and disability, frailty, and CLAD. For example, cytokines such as interleukin-1 beta play fundamental roles in both sleep regulation and lung transplant rejection. While plausible, disturbed sleep could reflect a common unmeasured latent factor driving our observed associations. Thus, these potential biobehavioral explanations should be considered speculative until more definitive research is performed.

Because this pilot survey effort focused on lung transplant recipients, beyond BiPAP/CPAP use (e.g., use of sleep medications, patient-reported sleep problems, etc.), we lack information on whether sleep problems and cognitive dysfunction predated transplant surgery. We also do not have reliable information on which, if any, treatments were attempted to address sleep problems. While these limitations do not detract from our observed associations, they do highlight considerations for future study designs that would capture the preoperative and perioperative data needed to answer these questions. Knowledge of these data also carries implications for future intervention design. Our

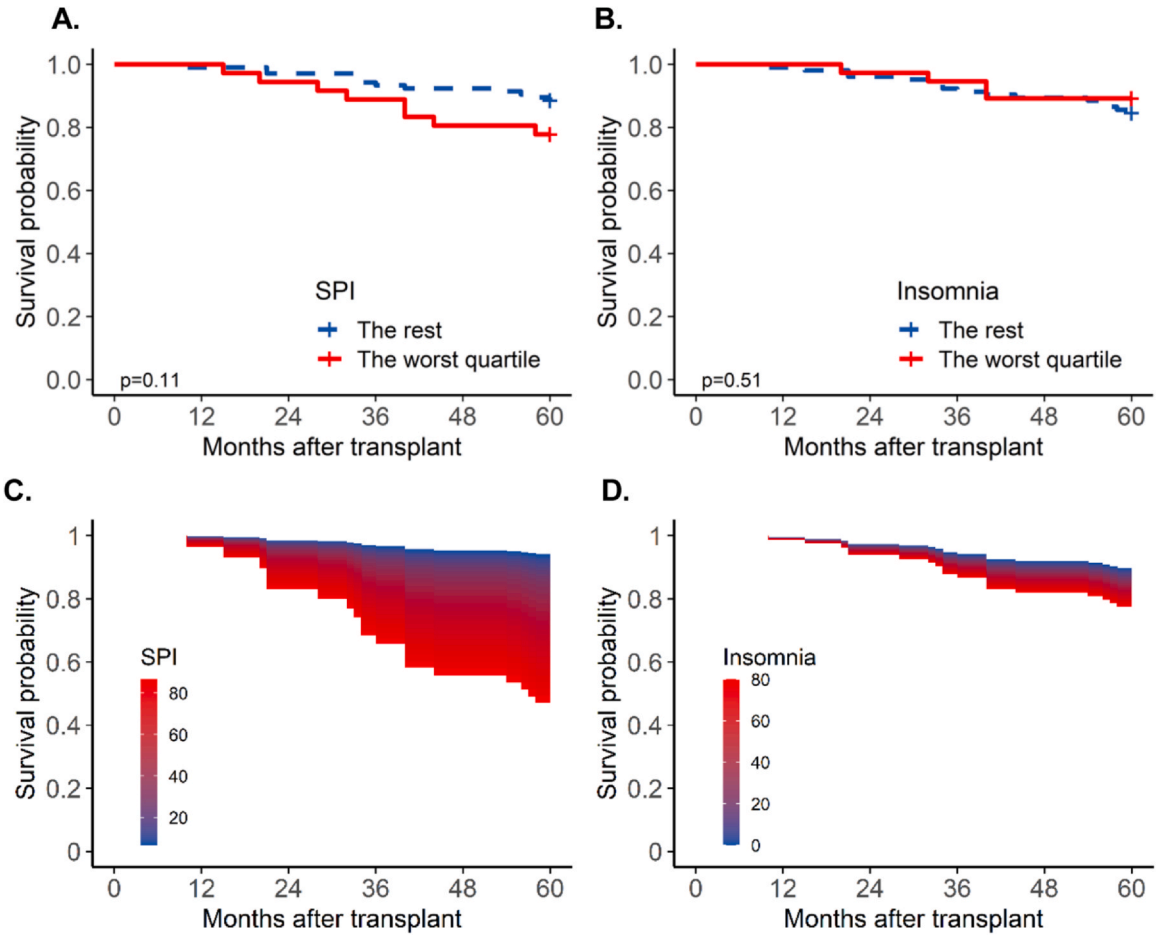

Figure 2 Kaplan-Meier estimate of the association of disturbed sleep by MOS-Sleep Problems Index (A) and insomnia-specific subscale (B) defined as categorical variables on time to death. Survival area plot illustrating the association of disturbed sleep by MOS-Sleep Problems Index (C) and insomnia-specific subscale (D) defined as continuous variables on time to death. MOS, Medical Outcomes Study; SPI, Sleep Problems Index.

convenience sampling strategy yielded a group of participants whose sleep was queried over a range of early postoperative years potentially limiting our ability to identify important perioperative and postoperative predictors of poor sleep after transplant. Although our 86% response rate is generally considered excellent and most of the missing surveys were missing at random, it is possible that the few missing not at random surveys could have introduced bias. We suspect that any bias from these missing not at random surveys would have likely biased us toward the null. For missing surveys to have biased us away from the null would have required that those with poorer sleep *and* missing not at random surveys had *better* quality of life, cognitive function, physical functioning, and reduced risk of CLAD and death. While speculative, we suspect that this potential negative association between sleep and our outcomes of interest is unlikely. We also lack information on the causes of sleep disturbances or how they change over the early postoperative period. In prior work by our team and by others, other factors after transplant improved for many in the first postoperative year. Whether *persistently* poor sleep is differentially associated with clinical outcomes than sleep that worsens or improves over time is unknown. Answers to this unknown are important when considering when to screen for sleep before or after transplant and when designing potential interventions. The effect estimates from our exploratory analyses suggest that the associations between poor sleep and HRQL, CLAD, and death *may* persist whether poor sleep is reported early or later after transplant, but the wide CIs limit our ability to make strong inferences. We also did not perform objective tests of sleep, which precluded us from determining which type of sleep impairment drove our findings. This has critical treatment implications as cognitive behavioral and pharmacologic interventions used to treat problems such as insomnia are less effective for sleep-disordered breathing conditions. Importantly, cognitive behavioral therapy is the first-line treatment for treating insomnia and is not often employed in the lung transplant population.[53] While our insomnia subscale has face validity, we did not use a validated insomnia-specific measure. Thus, our findings related to insomnia should be interpreted with caution. Finally, although this cohort represents one of the largest studies of sleep after lung transplantation, it, nevertheless, is relatively modest in size.

Future efforts to study sleep longitudinally in the perioperative and early postoperative period may help shed light on the causal role of sleep in lung transplant recovery.

If our early findings are confirmed, treatments for disturbed sleep attributable to disorders such as insomnia and obstructive sleep apnea are effective, relatively easy to implement, and could be incorporated into post-transplant care both in person and remotely. Further, if our findings linking disturbed sleep with CLAD and mortality are confirmed, efforts to disambiguate their behavioral or immunological underpinnings could shed new insights into important outcomes in lung transplantation.

Disclosure statement

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Author Contributions

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors made the following contributions.

- A.P., J.P.S., Y.G., and C.Y.H. made substantial contributions to the conception and study design.
- J.P.S. acquired the research funding for the study.
- J.P.S., Y.G., C.Y.H., A.V., R.K., A.S., and L.B. made substantial contributions to the acquisition, analysis, or interpretation of data for the work.
- A.P. and J.P.S. wrote the first draft of the article. All authors revised the manuscript for important intellectual content.
- All authors approved the article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100170.

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