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Sleep quality and its association with health-related quality of life of patients on lung transplantation waitlist in Japan

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Abstract

Purpose Poor quality of sleep is a common feature in patients with various lung diseases and affects their health-related quality of life (HRQL). We evaluated sleep quality and HRQL in patients on the waitlist for lung transplantation in Japan.

Methods In this prospective study, patient-reported and physiological data were collected from patients newly registered on the waitlist for lung transplantation in Japan. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI) and HRQL using the St. George's Respiratory Questionnaire (SGRQ). The frequency of poor sleep quality, correlations between sleep quality and various clinical parameters, and predictive factors of sleep quality were examined.

Results Of 193 patients, the three most-frequent indications for lung transplantation were interstitial pneumonia (n = 96), pulmonary complications of hematopoietic stem cell transplantation (n = 25), and pulmonary hypertension (n = 17). Poor sleep quality (PSQI > 5) was observed in 102 patients (53%) and was significantly associated with worse Hospital Anxiety and Depression Score (HADS), worse SGRQ score, worse modified Medical Research Council Dyspnea score, and shorter 6-min walk distance. However, it was not associated with sex, pulmonary function, interstitial pneumonia, or arterial blood gas. Stepwise multiple regression analysis indicated that poor sleep quality was explained significantly by HADS anxiety (23%) and SGRQ Symptoms (10%).

Conclusion Poor sleep quality was found to be common among patients on the lung transplantation waitlist in Japan. The two most significant factors responsible for impaired sleep quality were anxiety and respiratory symptoms. Additional care should be taken to ensuring a better quality of sleep for such patients.

Keywords Lung transplantation · Sleep quality · Health-related quality of life (HRQL) · Pittsburgh Sleep Quality Index (PSQI) · St. George's Respiratory Questionnaire (SGRQ)

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Introduction

Patients with different lung diseases also suffer from poor sleep quality, which impacts their health-related quality of life (HRQL) [1–4]. Although these mechanisms are various according to the underlying diseases, relaxed respiratory muscle, reduced effective lung volume, and occasional associated desaturation during sleep may worsen sleep quality or nocturnal symptoms.

Lung transplantation has been recognized as an effective treatment for patients with end-stage lung diseases. Considering that the condition of disease in these patients is usually very severe, it is assumed that their sleep will be impaired. Several studies carried out in Western countries have reported an increased incidence of poor sleep quality among lung transplantation candidates [5–10]. However, thus far, there are no studies focusing on sleep quality in lung transplantation candidates in Japan. In particular, owing to severe donor shortage, the average waitlisted time in Japan is over 800 days, which is longer than those reported in other countries [11, 12]. Therefore, maintaining HRQL and sleep quality during this period is vital.

We anticipate that patients waitlisted for lung transplantation would have a high prevalence of poor sleep quality and that it would be associated with their impaired HRQL. This can be assumed likewise for both Japan and Western countries. We also think that analyzing factors related to sleep quality could reveal outcomes to be considered in pursuit of potential approaches to improve sleep quality or HRQL. While we usually tend to observe mainly physiological parameters such as pulmonary function during the management of those patients, we would like to demonstrate the importance of also taking into account patient-reported measures including sleep quality.

We hypothesized that sleep quality in patients on lung transplantation waitlist in Japan would be affected by disease severity and an impaired psychological status. Subsequently, we cross-sectionally assessed their sleep quality and its association with clinical variables, including HRQL.

Some of the results of this study have previously been presented as a conference abstract [13].

Methods

Patients

In this prospective study, we recruited 193, newly waitlisted patients for lung transplantation during the period from 2009 and 2015. We have obtained approvals from the institutional ethical boards of the Tohoku University Hospital, the Kyoto University Hospital, and the Okayama University Hospital for this study. Written informed consent was obtained from all the recruited patients. Exclusion criteria were previous history of heart and lung transplantation or age under 17 years. The database was the same as our previous study [14].

We assessed all the patients at the time of registration on the waitlist for pulmonary function, arterial blood gas, and patient-reported measurements of sleep quality, HRQL, dyspnea, and psychological status. Pulmonary function was assessed by measuring forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). Additionally, a 6-min walk test and the distance (6MWD) were recorded for stable patients.

Patient-reported measurements

The Japanese version of the Pittsburgh Sleep Quality Index (PSQI) was used to evaluate patients' sleep quality [15–18]. It assesses the quality of sleep over an interval of 1-month time. In this test, 19 separate points generate 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction). Each of these dimensions was given a score between 0 and 3, followed by summing up of the 7 component scores to get a global PSQI score. This score ranges from 0 to 21 where higher scores show poor status and cutoff score of > 5 indicates poor sleep quality [15, 17].

The Japanese version of the St. George's Respiratory Questionnaire (SGRQ) was used to evaluate patients' HRQL [19]. The SGRQ is most often used for determining respiratory-specific HRQL in lung transplantation waitlisted patients [14, 20, 21]. The questionnaire includes three components of the Symptoms, Activities, and Impacts, and then the Total score is determined. The range of the score is from 0 to 100, with elevated scores indicating a worse HRQL.

The modified Medical Research Council (mMRC) dyspnea scale [22, 23] was used to evaluate dyspnea during activities of daily living. The mMRC dyspnea scale is a unidimensional 5-point scale (0–4) that is set on the basis of the levels of different dyspnea inducing physical activities. Dyspnea is considered worse if the scores are high. The Japanese version of the Hospital Anxiety and Depression Scale (HADS) was employed [22, 24] for assessing the psychological status of the patients, as this test determines levels of depression and anxiety. The range of each subscale is from 0 to 21, and a poor psychological status is indicated by higher score.

Statistical analysis

The results are shown as the mean ± standard deviation. Relationship between two data sets is determined using Spearman rank correlation tests. Variables that can best predict the PSQI score were determined using stepwise multiple regression analyses, employing the factors that significantly correlate with PSQI score as explanatory variables. A p value

< 0.05 is considered statistically significant. All statistical analyses were conducted with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). [14, 25].

Results

Patients

The characteristics of the 193 patients (97 males) included in this study are shown in Table 1. The indications for lung transplantation were as follows: interstitial pneumonia (IP) ($n = 96$, 49.7%), pulmonary complications of hematopoietic stem cell transplantation ($n = 25$, 13.0%), pulmonary hypertension ($n = 17$, 8.8%), lymphangioleiomyomatosis ($n = 15$, 7.8%), chronic obstructive pulmonary disease (COPD) ($n = 13$, 6.7%), bronchiectasis ($n = 12$, 6.2%), and others ($n = 15$, 7.8%). Notably, 87 patients (45.1%) were treated with an oral corticosteroid. Long-term oxygen therapy was provided to 170 (88.1%) patients, and 9 (4.7%) patients received home noninvasive ventilation.

Table 1 Characteristics of 193 patients

	Mean ± SD, or number
Age, years	45.4 ± 10.5
Sex, male/female	97/96
BMI, kg/m^2	19.6 ± 3.9
Usage of corticosteroid	87
Hemoglobin, g/dL	13.2 ± 0.2
Albumin, g/dL	7.2 ± 3.4
C-reactive protein, mg/dL	0.67 ± 0.12
PaO_2, mmHg	78.8 ± 25.9
$PaCO_2$, mmHg	45.9 ± 9.6
FEV_1, %predicted	41.3 ± 19.8
FVC, %predicted	50.8 ± 21.1
6MWD, *m*	302 ± 144
mMRC dyspnea (0–4)	2.7 ± 1.1
HADS anxiety (0–21)	5.5 ± 4.1
HADS depression (0–21)	6.8 ± 4.6
PSQI (0–21)	6.8 ± 3.9
SGRQ Symptoms (0–100)	66.8 ± 19.0
SGRQ Activities (0–100)	83.1 ± 14.1
SGRQ Impacts (0–100)	56.9 ± 19.0
SGRQ Total (0–100)	66.5 ± 15.2

The numbers in parentheses show theoretical score range. *6MWD*, 6-min walk distance; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Scale; *mMRC*, modified Medical Research Council; *$PaCO_2$*, partial pressure of arterial carbon dioxide; *PaO_2*, partial pressure of arterial oxygen; *PSQI*, Pittsburgh Sleep Quality Index; *SGRQ*, St. George's Respiratory Questionnaire

PSQI scores and relationship with clinical measurements

Figure 1 shows the frequency distribution histograms of the PSQI score. The mean score of the PSQI was 6.8 ± 3.9, and poor sleep quality was seen in 102 patients (52.8%). Each correlation between the PSQI score and other clinical parameters is shown in Table 2. The PSQI score was not significantly correlated with age, sex, body mass index, IP or non-IP, usage of a corticosteroid, and blood parameters such as hemoglobin, albumin, and C-reactive protein ($p > 0.05$). Similarly, it was not correlated with pulmonary function (i.e., FVC (%predicted) and FEV_1 (%predicted)), arterial blood gas parameters (i.e., of partial pressure of arterial oxygen and carbon dioxide) ($p > 0.05$). However, it demonstrated a weak yet significant correlation with 6MWD (Spearman rank correlation coefficient (Rs) = − 0.24, $p = 0.001$).

The PSQI score was found to significantly correlate with mMRC dyspnea (Rs = 0.28, $p < 0.001$) and also with anxiety (Rs = 0.50, $p < 0.001$) and depression (Rs = 0.46, $p < 0.001$) of the HADS. Regarding HRQL, the PSQI score was moderately significantly correlated with the SGRQ Symptoms, Activities, Impacts, and Total score (Rs = 0.41, 0.32, 0.47, and 0.48, respectively; $p < 0.001$) (Fig. 2). However, scatter plots indicated that these associations were significant but varied.

Moreover, we subsequently performed multiple regression analysis for investigating the factors predicting the PSQI score. As shown in Table 3, 33% of the variance in the PSQI score was explained in the present models. HADS anxiety and SGRQ Symptoms significantly accounted for 23% and 10% of the variance, respectively.

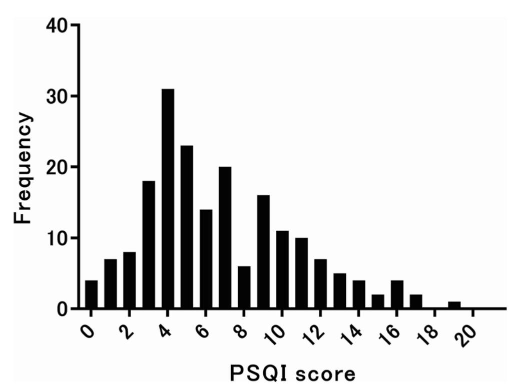

Fig. 1 Frequency distribution of PSQI score. *PSQI*, Pittsburgh Sleep Quality Index

Table 2 Relationship between PSQI and clinical measurements

	Correlation coefficient
Age	0.04
Sex	0.04
BMI	0.01
Interstitial pneumonia	− 0.06
Corticosteroid use	− 0.04
Hemoglobin	0.12
Albumin	0.03
CRP	0.11
FEV_1	− 0.13
FVC	− 0.15
PaO_2	0.02
$PaCO_2$	0.09
6MWD	− 0.24*
mMRC dyspnea	0.28*
HADS anxiety	0.50*
HADS depression	0.46*
SGRQ Symptoms	0.41*
SGRQ Activities	0.32*
SGRQ Impacts	0.47*
SGRQ Total	0.48*

*$p < 0.05$

6MWD, 6-min walk distance; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Scale; *mMRC*, modified Medical Research Council; *$PaCO_2$*, partial pressure of arterial carbon dioxide; *PaO_2*, partial pressure of arterial oxygen; *PSQI*, Pittsburgh Sleep Quality Index; *SGRQ*, St. George's Respiratory Questionnaire

Discussion

In this study, we analyzed sleep quality in candidates on the waitlist for lung transplantation in Japan. This study revealed the following: (1) more than half of the patients had poor sleep quality (PSQI > 5); (2) unlike pulmonary function, the SGRQ score was significantly associated with the PSQI score; and (3) respiratory symptoms and anxiety showed a significant relationship with a poor PSQI score in a multivariate analysis.

Regarding the frequency of poor sleep quality, it was present in 51.2% of the patients waitlisted for lung transplantation. Studies in Western countries have reported that the frequency of impaired sleep quality among lung transplantation candidates was 31.7–54.5% [5–7], which is compatible with our findings. Among the Japanese general population, the frequency of poor sleep quality was reportedly 26.4–31.1% [17]. Therefore, impaired sleep quality appears to be more common in lung transplantation candidates. Additionally, as a characteristic of Japan, the waitlist time is longer than Western countries [11, 12]. Therefore, it is necessary to observe and ensure the sleep quality of such patients.

Next, the relationships between the PSQI score and the SGRQ scores were all moderately significant (Rs = 0.32–0.48). Generally, dyspnea and psychological status play more important roles in HRQL of patients with advanced respiratory diseases than physiological measurements [14, 26, 27]. However, we showed that sleep quality might also be a critical factor in determining their HRQL. Poor sleep quality was reported to be associated with various lung diseases, including idiopathic pulmonary fibrosis [1], COPD [2], pulmonary hypertension [3], and cystic fibrosis [4]. The mechanisms involved in these processes are multifactorial. However, these must not be overlooked, because patients waitlisted for lung transplantation have various severe underlying diseases and comorbidities. In addition, in the present patients, an unstable psychological status prior to lung transplantation leads to sleep disturbance, which in turn may be related to worse HRQL [28]. Thus, as the scatter plots in the figures showed that the associations between the PSQI and the SGRQ were significant but varied, physicians must carefully cope with the problems of sleep quality individually.

In multivariate analysis, we demonstrated that anxiety and respiratory symptoms were significantly associated with sleep quality. Psychological factors seem to be important in explaining sleep quality in organ transplant candidates [5, 6]. Reilly–Spong et al. indicated that anxiety, depression, and fatigue were predictive factors of sleep impairment in such patients [5]; Fatigati et al. revealed a correlation between the mental component of the Short Form 36-item Health Survey Questionnaire, female sex, and sleep disorder in lung transplant recipients [6]. Although confirmed evidence is still lacking, pulmonary rehabilitation, cognitive behavioral therapy, relaxation therapy, antidepressants, palliative therapy, etc., may be considered to reduce anxiety for patients with such severe advanced lung diseases, which may lead to improving sleep quality or HRQL. Furthermore, a study in a general population showed that respiratory symptoms are more associated with sleep complaint than lung function or a respiratory diagnosis [29], which is consistent with the present study in lung transplant candidates. Therefore, efforts should be exerted to control the respiratory symptoms, aiming to maintain or improve sleep quality.

On the other hand, physiological measurements (i.e., pulmonary function or arterial blood gas) were not significantly correlated with sleep quality measured by the PSQI score. This finding was consistent with those of previous reports regarding the relationship between these measurements and sleep quality in patients with various respiratory diseases [1, 2, 4]. However, in current practice, treating physicians tend to pay attention to physiological measurements rather than patient-reported measurements in the management during waiting time. Care regarding the mental status, respiratory symptoms, and sleep of patients, in addition to physiological conditions, would also be crucial for improved management.

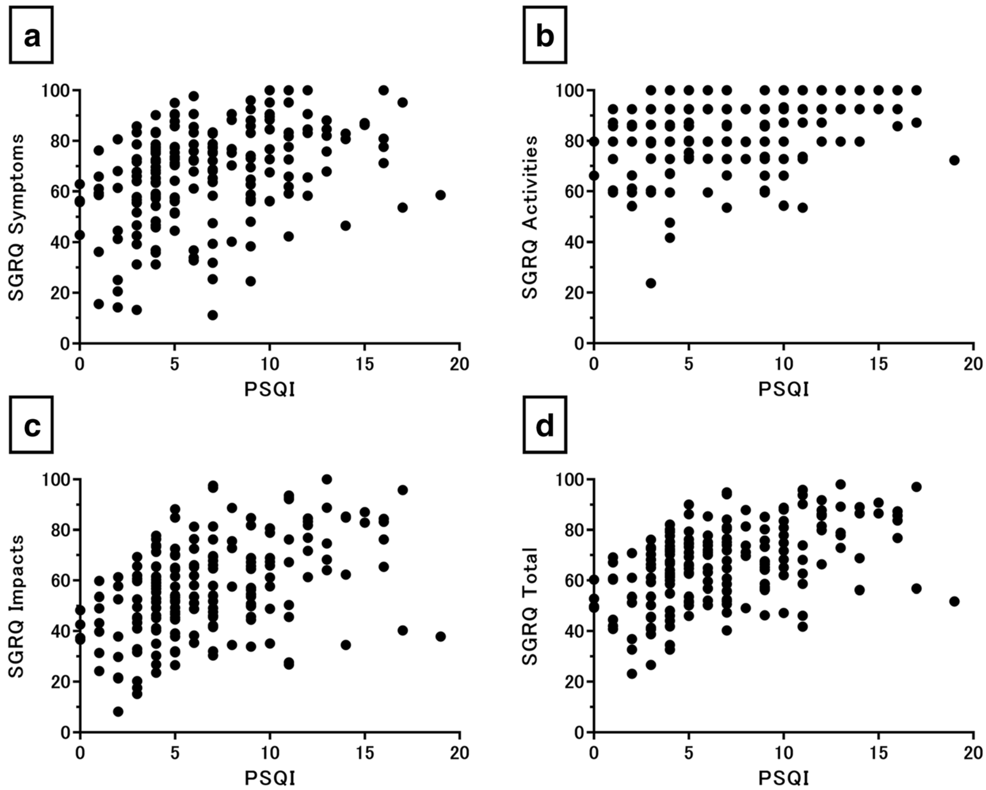

Fig. 2 Scatter plots between the PSQI versus the SGRQ Symptoms (a), Activities (b), Impacts (c), and Total (d). *PSQI*, Pittsburgh Sleep Quality Index; *SGRQ*, St. George's Respiratory Questionnaire

Although sleep quality exhibits a significant relationship with HRQL, recent studies [30, 31] have suggested that it also possesses predictive properties of future outcomes. Namely, a poor PSQI score was significantly associated with exacerbations of COPD [30, 31]. Therefore, although it has not been proven in other respiratory diseases, assessing and better managing the sleep quality of patients waitlisted for lung transplantation may exert beneficial effects on disease exacerbation or mortality, while waitlist mortality is still a significant problem [32].

This study had several limitations. First, sleep quality was assessed only at the time of registration on the waitlist. Longitudinal studies that monitor transitional changes in sleep quality for longer periods of time and studies comparing pre-lung transplantation with post-lung transplantation sleep quality are warranted in the future. At least, we observed that HRQL of patients waitlisted for lung transplantation deteriorated over 1 year [14]. Second, several studies indicated that sleep-disordered breathing (SDB) is common among lung transplant recipients [8–10, 33–36]. Although the co-presence of undiagnosed SDB may be related to worsened sleep quality, we did not assess this hypothesis in the present study. Treatment of SDB may have a beneficial impact on poor sleep quality, as well as the severe underlying lung disease [35, 36]. Therefore, further studies are required to investigate the role of SDB in this setting. Similarly, objective sleep measurements including polysomnography or actigraphy were not included in the present study, indicating that it lacks proper sleep-medical diagnostic procedures. Subjective sleep quality can be affected by different sleep disorders, including insomnia, obstructive sleep apnea, and movement disorders. Therefore, we would like physicians involved in this field to regard subjective sleep complaints from the patients as the first trigger for sleep evaluation, sleep diagnosis, and specific treatment for sleep disorders. Finally, although HADS anxiety and SGRQ Symptoms remained significant factors related to

Table 3 Stepwise multiple regression analyses to predict the PSQI score

	PSQI
6MWD	–
mMRC dyspnea	–
HADS anxiety	0.23
HADS depression	–
SGRQ Symptoms	0.10
SGRQ Activities	–
SGRQ Impacts	–
SGRQ Total	–
Cumulative R^2	0.33

All values indicate coefficient of determination (R^2). Missing values (–) showed no significant relationships. *6MWD*, 6-min walk distance; *HADS*, Hospital Anxiety and Depression Scale; *mMRC*, modified Medical Research Council; *PSQI*, Pittsburgh Sleep Quality Index; *SGRQ*, St. George's Respiratory Questionnaire the PSQI score in multiple regression analysis, they explained only 33% of the variance, indicating that other potential factors such as SDB might have been missing. Based on the present study, more appropriate models using more suitable variables and methodology should be explored in the future.

Conclusions

Poor sleep quality was common in lung transplantation waitlisted patients in Japan. Thus, it is essential to assess sleep quality and HRQL in addition to physiological measurements and to pay more attention to anxiety and respiratory symptoms as the key contributive aspects to maintain sleep quality in such patients.

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Compliance with ethical standards

Conflict of interest KC received lecture fees from Philips-Respironics. The Department of Respiratory Care and Sleep Control Medicine, Graduate School of Medicine, Kyoto University, was previously funded by endowments from Philips-Respironics, Teijin Pharma, Fukuda Denshi, and Fukuda Lifetec Keiji, and is now by Philips-Respironics, Resmed Japan, Fukuda Denshi, and Fukuda Lifetec Keiji, to Kyoto University. We declare that no funding sources influenced the preparation of the any part of this manuscript including collection, interpretation, and presentation of the data.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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