Article published online: 2024-02-15

Sleep Restfulness in Patients with Obstructive Sleep Apnea Undergoing Continuous Positive Airway Pressure Therapy

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Sleep Sci 2024;17(1):e37–e44.

Abstract

Objective Sleep restfulness is closely associated with mortality. Thus, it is an important sleep-related symptom in the general population. However, it is rarely evaluated in patients with obstructive sleep apnea (OSA) syndrome. The present study examined the importance of sleep restfulness in patients with OSA receiving continuous positive airway pressure (CPAP) therapy.

Materials and Methods We administered sleep-related questionnaires, which included items such as subjective sleep duration and sleep restfulness, to 775 patients with OSA receiving CPAP therapy. Sleep restfulness was rated using a 5-point Likert-type scale, with the score of 5 indicating restfulness. Good adherence to CPAP therapy was defined as the use of CPAP therapy for at least 4 h per night in 70% of nights.

Results We excluded 105 patients with lacking data. Thus, 670 patients were finally examined. In total, 29 (4.3%), 124 (18.5%), 139 (20.8%), 235 (35.1%), and 143 (14.3%) patients answered restless (1), somewhat restless (2), neither (3), somewhat restful (4), and restful (5) respectively. A total of 467 (69.7%) patients had good adherence to CPAP therapy. Multivariate logistic regression analysis showed that sleep restfulness was independently and positively associated with subjective sleep duration ($\geq$ 7 hours) and good adherence to CPAP therapy.

Conclusion Sleep restfulness was associated with subjective sleep duration and good adherence to CPAP therapy in patients with OSA. Favorable outcomes are significantly correlated with good adherence to CPAP therapy. Thus, sleep restfulness can be an indicator of a subtype that has favorable outcomes in patients after CPAP therapy.

Keywords
- continuous positive airway pressure
- obstructive sleep apnea
- surveys and questionnaires

received
December 11, 2022
accepted
May 8, 2023

DOI https://doi.org/10.1055/s-0043-1776741.
ISSN 1984-0659.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder that affects more than 900 million adults aged between 30 and 69 years worldwide.[1] It is characterized by pathophysiological features, such as repetitive episodes of breathing cessation during sleep, resulting in intermittent and/or sustained hypoxemia and sleep disruption.[2] These pathophysiological features are closely associated with several comorbidities of OSA, including hypertension, cardiovascular diseases, arrhythmias, stroke, and neurocognitive disorders.[3,4] Continuous positive airway pressure (CPAP) therapy, which is the gold standard treatment for OSA, has favorable outcomes, such as short and long-term decreased blood pressure[5–7] and reduced stroke risk,[8] depending on good adherence to this therapy. Meanwhile, the effect of CPAP therapy on cardiovascular events is controversial.[9,10]

The pathophysiological features of OSA also cause sleep-related symptoms, including snoring, insomnia, sleep restlessness, excessive daytime sleepiness, falling asleep, and headache. Excessive daytime sleepiness adversely affects everyday activities and is associated with an increased risk of motor vehicle and occupational accidents.[4] Moreover, it increases the risk of mortality in elderly patients with OSA.[11] Excessive daytime sleepiness can be assessed by objective measures, such as the Maintenance of Wakefulness Test (MWT) and the Multiple Sleep Latency Test (MSLT), and self-reported (subjective) measures, such as the Epworth Sleepiness Scale (ESS), the Basic Nordic Sleepiness Questionnaire, and the Stanford Sleepiness Scale.[12,13] The ESS is the most widely used tool for assessing subjective sleepiness. The ESS scores do not correlate well with OSA severity,[14–16] but correlate closely with the MWT and MSLT.[16] The poor correlation of the ESS with OSA may be partially due to the heterogeneity of OSA.

Regarding the heterogeneity of OSA, patients with OSA experience combined sleep-related symptoms and comorbidities, changes in apnea–hypopnea index (AHI), and symptoms in response to CPAP therapy. Furthermore, they present with different outcomes after CPAP therapy.[17,18] Thus, in recent years, cluster analysis based on sleep-related symptoms is performed to characterize the disease subtypes of OSA, such as disturbed sleep, minimally symptom, and excessive daytime sleepiness.[18–23] Attention has been paid to the subtype of excessive daytime sleepiness because this subtype is associated with a higher risk of cardiovascular events.[19–22] However, it was not simply classified using the ESS.[20,24] In addition, the sleep-related symptoms that should be included in the cluster analysis of OSA are unknown. Previous studies showed that sleep restfulness was associated with a risk of cardiovascular diseases,[25] and it influenced mortality according to age and sleep duration.[26] Thus, sleep restfulness is an important sleep-related symptom in the general population. However, it is rarely included in sleep-related questions in cluster analysis of OSA.[23] Thus, the role of sleep restfulness in patient with OSA is unknown. We hypothesized that sleep restfulness closely correlates with adherence to CPAP therapy in patients with OSA. Thus, the current study examined the role of sleep restfulness in patients with OSA undergoing CPAP therapy.

Materials and Methods

Participants

We administered sleep-related questionnaires to 775 patients with OSA who received CPAP therapy from April 2022 to July 2022 and who were followed-up at Kyoto University Hospital. The present study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval no. R3618, approval date: July 22, 2022). The need to obtain a written informed consent for all participants was waived off.

Data on clinical characteristics, including age, body mass index (BMI), smoking status, comorbidities (hypertension, dyslipidemia, diabetes mellitus, cardiovascular diseases, arrhythmia, stroke, and epilepsy), and AHI before CPAP therapy initiation, and duration after CPAP therapy initiation, were obtained from the medical records.

CPAP Therapy and Devices

Data on CPAP therapy, such as CPAP devices (Philips Respironics or ResMed device), pressure settings (autoadjusting or fixed), and interfaces, were obtained from the medical records. Information on AHI, CPAP usage time, and mask leak was obtained using Encore Pro 2 or Care Orchestrator (Philips Respironics), ResScan (ResMed), NemLink (Teijin Pharma Ltd), or f'Rens (Fukuda Densi Ltd). Data were downloaded for 1 month before the sleep-related questionnaires were administered. Adherence to CPAP therapy (good adherence) was defined as the use of CPAP therapy for at least 4 h a night in 70% of nights for 1 month.[27] Residual AHI was defined as AHI $\geq$ 10 events/hour.[27] Large leaks were defined as large leaks lasting $>$ 1 hour if Philips Respironics devices were used;[27] and a 95th percentile leak $>$ 24 L/minute with the nasal or pillow interface or $>$ 36 L/minute with the oronasal interface if ResMed devices were used.[27]

Sleep-related Questionnaire

Questions of the Japanese version of the ESS (JESS), subjective sleep duration, sleep restfulness, and use of sleep medications within the last month were included in the sleep-related questionnaire.

The JESS is used to assess daytime sleepiness and is a self-administered questionnaire with eight questions.[28] Patients were instructed to rate their usual chances of dozing off or falling asleep while engaged in eight different activities using a 4-point scale (from 0 to 3). The JESS score ranged from 0 to 24. If the score was higher, the risk of falling asleep during daytime was greater. A JESS score $\geq$ 11 indicated subjective excessive daytime sleepiness.

Sleep restfulness was rated using a 5-point Likert-type scale, with the score of 5 indicating restfulness (1 = restless; 2 = somewhat restless; 3 = neither; 4 = somewhat restful; 5 = restful).[26]

Statistical Analysis

Data were expressed as median with an interquartile range for continuous variables or frequencies for categorical variables. All statistical analyses were performed using a statistical software package (JMP Pro 14 software; SAS Institute, Cary, NC, United States). First, clinical characteristics, sleep-related questionnaire scores, CPAP therapy, and CPAP device parameters were analyzed according to sleep restfulness score via univariate analysis. The Kruskal–Wallis test and the chi-squared test were utilized to compare continuous variables and categorical variables, respectively. Second, multivariate logistic regression analysis was performed to identify which variables could best determine sleep restfulness. In addition to gender, variables with a *p*-value < 0.05 in the univariate analysis were used in the multivariate analysis. Continuous variables were categorized into quartiles, and the upper quartile was entered in the multivariate analysis. A *p*-value < 0.05 was considered statistically significant.

Results

Participants

►**Figure 1** presents the study flowchart. Out of the 775 patients who received the sleep-related questionnaire, 695 (89.7%) completed it. In addition, 25 patients were excluded due to lack of data on AHI before CPAP therapy initiation ($n = 9$), and CPAP device parameters ($n = 16$). Finally, 670 patients were examined.

►**Table 1** shows data on clinical characteristics, sleep-related questionnaire scores, CPAP therapy, and CPAP device parameters. The cohort included 525 (78.4%) men and 145 (21.6%) women. The average BMI of the patients was of 26.8 (24.2–29.9) kg/m^2, and they presented comorbidities, such as hypertension (66.4%), dyslipidemia (51.2%), diabetes mellitus (27.3%), cardiovascular diseases (22.1%), arrhythmia (18.4%), stroke (9.9%), and epilepsy (2.7%). In total, 151 (22.5%) patients used sleep medications. Furthermore, 582 (86.9%) patients had a JESS score < 11 (no subjective excessive daytime sleepiness). The Philips Respironics device was used in 362 patients (54.0%) and the ResMed device in 308 (46.0%). Regarding CPAP device parameters, the AHI was 2.1 (1.1–3.6) events/hour, and 15 (2.2%) patients had residual AHI. A total of 467 patients (69.7%) had good adherence to CPAP therapy. In terms of restfulness, 29 (4.3%), 124 (18.5%), 139 (20.8%), 235 (35.1%), and 143 (14.3%) patients answered restless, somewhat restless, neither, somewhat restful, and restful, respectively.

Sleep Restfulness

►**Table 1** shows the differences in terms of clinical characteristics, sleep-related questionnaire scores, CPAP therapy, and CPAP device parameters according to sleep restfulness score. The subjective sleep duration (►**Figure 2A**) and mean CPAP duration (►**Figure 2B**) significantly increased with greater sleep restfulness score (from 1 to 5) (5 [4–6] hours; 6 [5–6.5] hours; 6 [5–6.5] hours; 6.5 [5.7–7] hours; and 7 [6–8] hours; $p < 0.0001$; and 4.6 [3.8–5.6] hours/days; 5.3 [4.1–6.1] hours/days; 5.5 [4.6–6.4] hours/days; 5.9 [4.9–6.6] hours/days; and 6.3 [5.4–7.1] hours/days; $p < 0.0001$ respectively). In addition, the percentage of patients using sleep medications (►**Figure 2C**) significantly decreased with greater sleep restfulness score (from 1 to 5) (48.3%; 28.2%; 24.5%; 19.2%; and 16.1%; $p = 0.002$ respectively). Meanwhile, the percentage of patients with a JESS score < 11 (►**Figure 2D**) and good adherence to CPAP therapy (►**Figure 2E**) significantly increased (58.6%; 77.4%; 84.2%; 91.1%; and 96.5%; $p < 0.0001$; and 44.8%; 57.3%; 64.8%; 72.8; and 85.3%; $p < 0.0001$ respectively).

►**Table 2** shows data on sleep restfulness based on the multivariate logistic regression analysis. Subjective sleep duration $\geq$ 7 hours, good adherence to CPAP therapy, mean CPAP duration of 6.6 hours/day, and JESS score < 11 were independently and positively associated with sleep restfulness. Meanwhile, the use of sleep medications was negatively associated with sleep restfulness.

Discussion

The present study showed that sleep restfulness was independently and positively associated with not only long

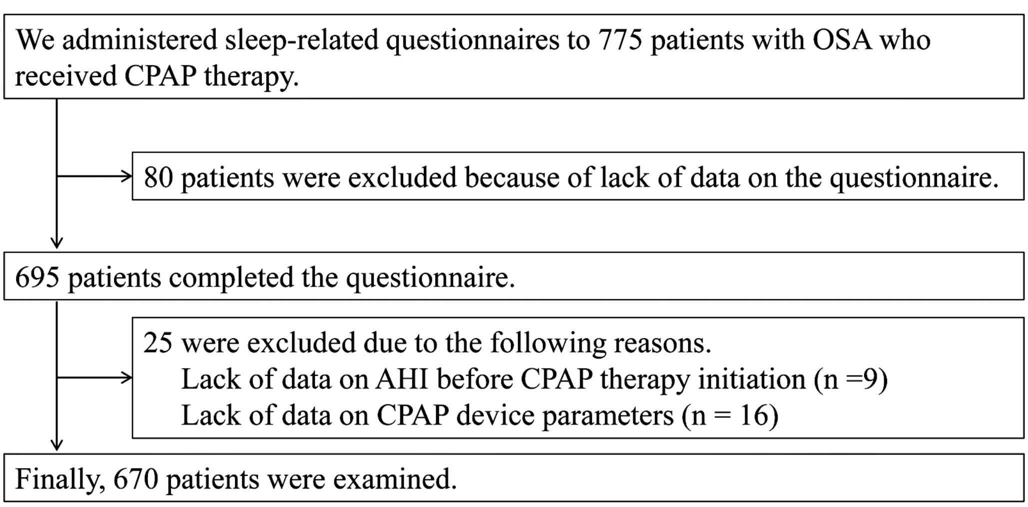

Fig. 1 Study flowchart. Abbreviations: AHI. apnea–hypopnea index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

Table 1 Differences in terms of clinical characteristics and data on sleep-related questionnaire, CPAP therapy, and CPAP device parameters according to sleep restfulness score.

	Total	Sleep restfulness score[a]					*p*-value[b]
		1	2	3	4	5	
Number	670	29	124	139	235	143	
Gender – male/female: *n* (%)	525/145 (78.4/21.6)	23/6 (79.3/20.7)	96/28 (77.4/22.6)	111/28 (79.9/20.1)	178/57 (75.7/24.3)	117/26 (81.8/18.2)	0.7
Age in years	69 (59–75)	57 (51–68)	64 (57–73)	68 (59–75)	70 (62–75)	71 (63–77)	< 0.0001
BMI in kg/m^2	26.8 (24.2– 29.9)	28.2 (26–30.6)	27.0 (24.4– 30.2)	26.7 (24.2– 30)	26.8 (24.1–30)	26.5 (24.4– 29.5)	0.61
Smoking history – never/past/current: *n* (%)	275/352/43 (41.1/52.5/6.4)	15/9/5 (51.7/31.0/17.3)	56/61/7 (45.2/49.2/5.6)	49/84/6 (35.3/60.4/4.3)	98/121/16 (41.7/51.5/6.8)	57/77/9 (39.8/53.9/6.3)	0.14
History							
Hypertension, *n* (%)	445 (66.4)	18 (62.1)	71 (57.3)	92 (66.2)	164 (69.8)	100 (69.9)	0.15
Dyslipidemia: *n* (%)	343 (51.2)	15 (51.7)	65 (52.4)	77 (55.4)	119 (50.6)	67 (46.9)	0.7
Diabetes mellitus: *n* (%)	183 (27.3)	11 (37.9)	34 (27.4)	39 (28.1)	59 (25.1)	40 (28.0)	0.7
Cardiovascular diseases: *n* (%)	148 (22.1)	8 (27.6)	26 (21.0)	26 (18.7)	48 (20.4)	40 (28.0)	0.33
Arrhythmia: *n* (%)	123 (18.4)	3 (10.3)	14 (11.3)	15 (10.8)	60 (25.5)	31 (21.7)	0.0004
Stroke: *n* (%)	66 (9.9)	2 (6.9)	12 (9.7)	17 (12.2)	24 (10.2)	11 (7.7)	0.74
Epilepsy: *n* (%)	18 (2.7)	0 (0)	2 (1.6)	5 (3.6)	6 (2.6)	5 (3.5)	0.56
Sleep-related questionnaire							
Sleep medication use: *n* (%)	151 (22.5)	14 (48.3)	35 (28.2)	34 (24.5)	45 (19.2)	23 (16.1)	0.002
Subjective sleep duration in hours	6 (5.5–7)	5 (4–6)	6 (5–6.5)	6 (5–6.5)	6.5 (5.7–7)	7 (6–8)	<0.0001
JESS score	5 (3–8)	9 (5–15)	7 (4–10)	5 (3–9)	5 (3–7)	3 (1–6)	<0.0001
JESS score <11: *n* (%)	582 (86.9)	17 (58.6)	96 (77.4)	117 (84.2)	214 (91.1)	138 (96.5)	<0.0001
Data on CPAP therapy							
AHI before CPAP therapy initiation–[c] events/hour	38.8 (27.3–51.6)	38.4 (31.9–62.3)	35.4 (25.7–47.8)	40.5 (27.6–56.1)	36.6 (26.2–48.8)	41 (29.7–53.1)	0.072
Duration after CPAP therapy initiation in years	6.5 (3.0–11.1)	6.5 (2.8–10.6)	6.8 (3.5–10.8)	7.2 (2.8–11.8)	5.9 (2.8–10.8)	6.1 (3.1–11.3)	0.57
CPAP devices – Philips Respironics/ResMed: *n* (%)	362/308 (54/46)	18/11 (62.1/37.9)	77/47 (62.1/37.9)	71/68 (51.1/48.9)	127/108 (54.0/46.0)	69/74 (48.3/51.8)	0.17
Pressure settings – autoadjusting/fixed: *n* (%)	634/36 (94.6/5.4)	27/2 (93.1/6.9)	114/10 (91.9/8.1)	128/11 (92.1/7.9)	228/7 (97.0/3.0)	137/6 (95.8/4.2)	0.15
Interface – nasal/pillow/ oronasal: *n* (%)	600/40/30 (89.5/6.0/4.6)	26/2/1 (89.7/6.9/3.4)	113/7/4 (91.1/5.7/3.2)	125/8/6 (89.9/5.8/4.3)	210/13/12 (89.4/5.5/5.1)	126/10/7 (88.1/7.0/4.9)	1.00

Table 1 (*Continued*)

	Total	Sleep restfulness score[a]					*p*-value[b]
		1	2	3	4	5	
CPAP device parameters							
AHI – events/hour	2.1 (1.1–3.6)	2.5 (1.4–4.1)	2.3 (1.2–4.2)	2.1 (1.1–3.3)	2.1 (1–3.6)	2 (1–3.4)	0.23
Mean duration of CPAP use on the days used: hours/day	5.7 (4.7–6.6)	4.6 (3.8–5.6)	5.3 (4.1–6.1)	5.5 (4.6–6.4)	5.9 (4.9–6.6)	6.3 (5.4–7.1)	<0.0001
Percentage of days of CPAP use: %	100 (86.7–100)	90.3 (73.4–100)	96.7 (76.9–100)	96.7 (73.3–100)	100 (90–100)	100 (96.7–100)	<0.0001
Large leaks:[d] *n* (%)	187 (27.9)	8 (27.6)	25 (20.2)	39 (28.1)	71 (30.2)	44 (30.8)	0.27
Good adherence:[e] *n* (%)	467 (69.7)	13 (44.8)	71 (57.3)	90 (64.8)	171 (72.8)	122 (85.3)	<0.0001

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; JESS, Japanese version of the Epworth Sleepiness Scale.
Notes: Data were expressed as median with an interquartile range for continuous variables or frequencies for categorical variables.
[a]Sleep restfulness was rated using a 5-point Likert-type scale, with the score of 5 indicating restfulness (1 = restless; 2 = somewhat restless; 3 = neither; 4 = somewhat restful; 5 = restful).
[b]Kruskal–Wallis test (continuous variables) or chi-squared test (categorical variables).
[c]Before CPAP therapy initiation, 577 (86.1%) patients underwent polysomnography, and 93 (13.9%) had a portable monitor.
[d]Large leaks were defined as large leaks lasting > 1 hour, if Philips Respironics devices were used; and a 95th percentile leak > 24 L/minute with the nasal or pillow interface or > 36 L/minute with the oronasal interface, if ResMed devices were used.
[e]Good adherence to CPAP therapy was defined as the use of CPAP therapy for at least 4 hours a night in 70% of nights for 1 month.

subjective sleep duration and a JESS score < 11 (no subjective excessive daytime sleepiness) but also good adherence to CPAP therapy. The favorable outcomes of CPAP therapy, such as decreased blood pressure and risk of cardiovascular diseases and stroke, significantly depend on good adherence to CPAP therapy.[5–10] Thus, sleep restfulness can be an indicator of a subtype that has favorable outcomes after CPAP therapy. However, sleep restfulness is rarely included in sleep-related questionnaires used in the cluster analysis of OSA.[23] In addition, sleep-related symptoms are largely influenced by sleep quantity (sleep duration), as shown in our study results. However, sleep duration has not been included in the cluster analysis of OSA. Therefore, sleep duration and restfulness should be included in the new cluster analysis of OSA to differentiate the heterogeneity of OSA.

Sleep restfulness was found to be independently associated with adherence to CPAP therapy. To the best of our knowledge, only one report showed the association between sleep restfulness and adherence to CPAP therapy in patients with OSA. Pien et al.[23] revealed that the longitudinal change in sleep restfulness (from restless to restful response to CPAP therapy) was larger in patients with good adherence to CPAP therapy than in those without in each subgroup such as disturbed sleep, minimally symptomatic, and sleepy classified via cluster analysis. Their results were consistent with ours. Sleep restfulness is closely associated with the risk of cardiovascular diseases and mortality.[25,26] Thus, it is an important sleep-related symptom in the general population. The favorable outcomes of CPAP therapy are significantly based on adherence to this therapy. Thus, future prospective studies should evaluate the association between outcomes and adherence to CPAP therapy in patients with or without sleep restful under receiving this therapy are needed to further identify the role of sleep restfulness in patients with OSA.

Sleep restfulness was independently associated with subjective sleep duration. Generally, sleep issue is assessed according to sleep quantity (sleep duration) and sleep quality (sleep-related symptoms). Regarding sleep duration, several systematic reviews have shown that short sleep duration is not only a predictor of mortality but also a possible marker of increased risk of hypertension, diabetes mellitus, cardiovascular diseases, and stroke.[29–32] Regarding sleep quality, several studies have shown that poor subjective sleep quality is associated with an increased risk of all-cause mortality and cardiovascular diseases.[25,26,33–35] In addition, sleep duration and sleep quality may affect health outcomes.[36] However, sleep duration has not been included in the cluster analysis of OSA. Thus, another cluster analysis of OSA including sleep duration must be developed.

Sleep restfulness was independently associated with nonusage of sleep medications. Although sleep medications can improve subjective sleep quality,[37,38] they have several adverse effects, including daytime fatigue, cognitive impairment, difficulty concentrating, oversleeping, and nightmares.[38,39] These adverse effects could have induced the lack of sleep restfulness in the present report, even if patients consumed sleep medications. However, it is not

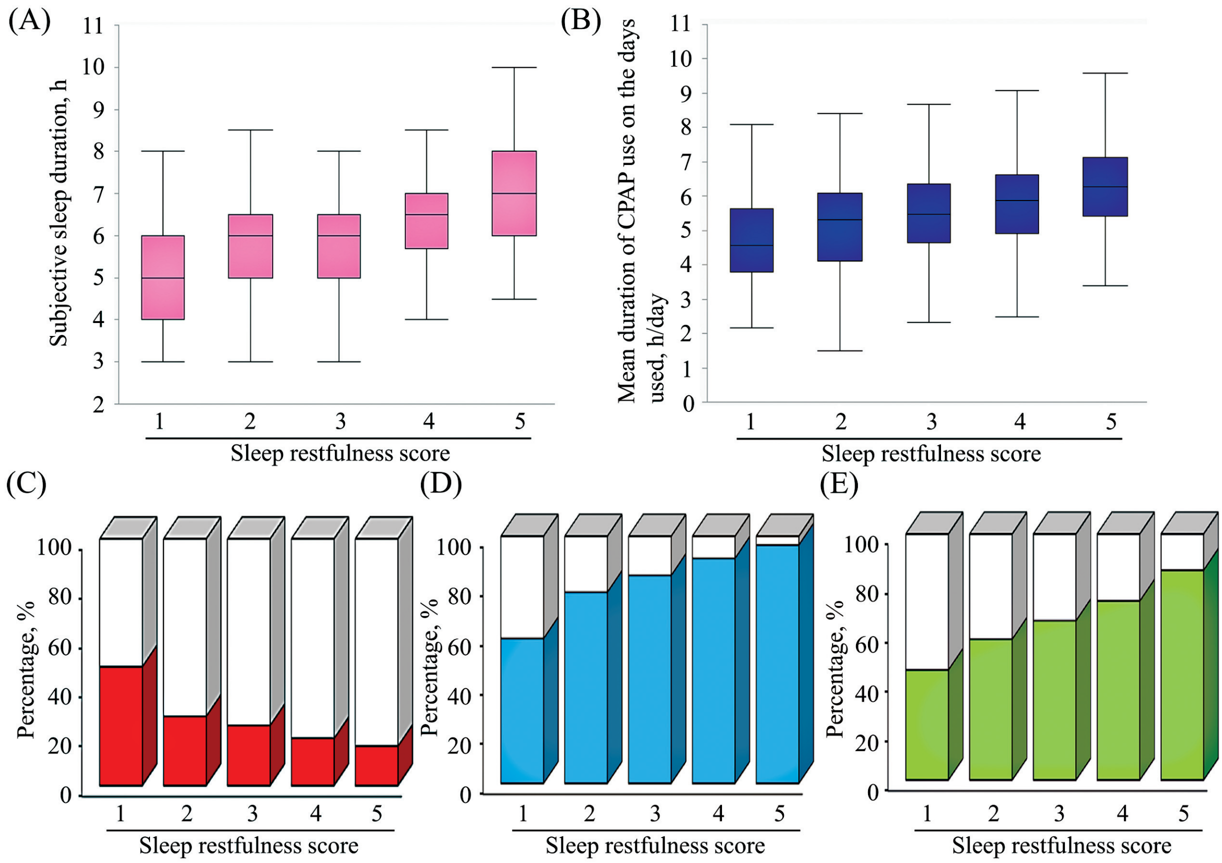

Fig. 2 Differences in terms of subjective sleep time (**A**), mean duration of CPAP use on the days used (**B**), and the percentage of sleep medication use (**C**), JESS score < 11 (**D**), and good adherence to CPAP therapy (**E**) according to sleep restfulness score. Abbreviations: CPAP, continuous positive airway pressure; JESS = Japanese version of the Epworth Sleepiness Scale.

recommended to discontinue sleep medications to get sleep restfulness.

The present study had several major limitations. First, this was a cross-sectional study. Thus, the present study did not validate the association between sleep restfulness and outcome. Second, 86.9% of the patients had a JESS score < 11. Hence, most patients did not complain of excessive daytime sleepiness. Third, the JESS questions, subjective sleep duration, sleep restfulness, and use of sleep medications were only included in the sleep-related questionnaire. Fourth, we did not evaluate types of sleep medications, such as benzodiazepines, nonbenzodiazepines, melatonin receptor agonist, antidepressants, antipsychotics, and anticonvulsants. Fifth, only subjective sleep duration was examined in the

Table 2 Multivariate logistic regression analysis of sleep restfulness.

	Model 1		Model 2		Model 3	
	Odds ratio (95%CI)	*p*-value	Odds ratio (95%CI)	*p*-value	Odds ratio (95%CI)	*p*-value
Age ≥ 75 years	1.48 (0.96–2.28)	0.078	1.58 (1.03–2.42)	0.036	1.47 (0.95–2.27)	0.082
Gender (male)	1.18 (0.71–1.96)	0.52	1.15 (0.70–1.91)	0.58	1.15 (0.69–1.92)	0.59
Arrythmia	1.01 (0.61–1.65)	0.98	1.03 (0.63–1.68)	0.92	1.03 (0.62–1.68)	0.84
Sleep medication use	0.48 (0.28–0.82)	0.0068	0.46 (0.27–0.78)	0.0042	0.46 (0.27–0.79)	0.0044
JESS score < 11	3.99 (1.55–10.25)	0.0041	4.12 (1.61–10.57)	0.0032	3.99 (1.55–10.31)	0.0042
Good adherence	2.27 (1.35–3.81)	0.0021	2.07 (1.21–3.54)	0.0076	1.95 (1.14–3.35)	0.015
Subjective sleep time ≥ 7 hours	2.69 (1.80–4.02)	< 0.0001	–	–	2.26 (1.46–3.49)	0.0003
Mean duration of CPAP use on the days used ≥ 6.6 hours/day	–	–	2.33 (1.51–3.60)	0.0001	1.64 (1.02–2.63)	0.042

Abbreviations: 95%CI, 95% confidence interval; CPAP, continuous positive airway pressure; JESS, Japanese version of the Epworth Sleepiness Scale.

present study. However, there is a difference between subjective and objective sleep duration.[40] Future prospective studies, which include several questions on sleep-related symptoms and examine kinds of sleep medications and objective sleep duration, must be conducted to identify the association among sleep-related symptoms, including sleep restfulness, sleep duration, and outcome.

Conclusion

Sleep restfulness was associated with subjective sleep duration and good adherence to CPAP therapy in patients with OSA. Thus, sleep restfulness can be an indicator of a subtype that has favorable outcomes after CPAP therapy.

Funding

The Department of Advanced Medicine for Respiratory Failure is a Department of Collaborative Research Laboratory funded by Teijin Pharma. The Department of Respiratory Care and Sleep Control Medicine is funded by endowments from Philips Japan, ResMed Japan, Fukuda Denshi and Fukuda Lifetec-Keiji to Kyoto University. This study was funded in part by the JSPS KAKENHI 22K16169 (SH).

Conflict of Interests

The authors have no conflict of interests to declare.

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