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Research Article

Threshold of the Periodic Limb Movements in Sleep and Periodic Limb Movements in Sleep with Arousal Indices

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ABSTRACT

Background: Periodic Limb Movements in Sleep (PLMS) and Periodic Limb Movements in Sleep with Arousal (PLMA) worsen sleep quality. To address the diagnostic values of the PLMS and PLMA indices, which worsen Polysomnography (PSG) outcomes, we performed Receiver Operating Characteristic (ROC) curve analyses.

Methods: Impaired PSG parameters were defined as Sleep Efficiency (SE) < 85%, Total Sleep Time (TST) < 360 min, and percentage of Wake After Sleep Onset (WASO) in sleep period time ≥ 15%.

Results: This retrospective study included 222 patients with a PLMS index ≥ 15 and an apnea-hypopnea index < 5 determined using PSG. ROC curve analyses showed that the thresholds of PLMS for decreased SE, decreased TST, and increased WASO were 28.8 (Area Under the Curve [AUC], 0.638; 95% Confidence Interval [CI], 0.563-0.714), 34.4 (AUC, 0.642; 95% CI, 0.569-0.715), and 34.5 (AUC, 0.646; 95% CI, 0.574-0.718), respectively. The thresholds of PLMA for decreased SE, decreased TST, and increased WASO were 4.00 (AUC, 0.632; 95% CI, 0.557-0.708), 5.16 (AUC, 0.612; 95% CI, 0.538-0.686), and 4.70 (AUC, 0.611; 95% CI, 0.537-0.685), respectively.

Conclusions: Patients with a PLMS index ≥ 28.8–34.5 and/or a PLMA index ≥ 4.00–5.16 independently had impaired PSG variables.

Keywords: Periodic Limb Movements in Sleep (PLMS); Periodic Limb Movements in Sleep with Arousal (PLMA); Impaired PSG variables; Receiver Operating Characteristic (ROC) curve analysis

INTRODUCTION

Periodic Limb Movements in Sleep (PLMS) is an independent disorder of repetitive, highly stereotyped limb movements that occur during sleep. This movement comprises dorsiflexion of the toes and ankles, accompanied by flexion of the knees, and sometimes of the hips. It is frequently observed in patients with Restless Legs Syndrome (RLS), narcolepsy, Rapid Eye Movement Sleep Behavior Disorder (RBD), and Obstructive Sleep Apnea (OSA) [1]. It has also been observed in several other medical conditions and in patients taking antidepressants and antipsychotics [2]. PLMS can also occur in generally healthy individuals, especially in men aged > 40 years [3-5].

In this study, PLMS was scored using Polysomnography (PSG). When PLMS was accompanied by arousal, it was referred to as PLMS with arousal index (PLMA). Periodic Limb Movement Disorder (PLMD) was defined as the presence of PLMS ≥ 15 times per hour in adults or PLMS ≥ 5 times per hour in children, with a complaint of insomnia and/or excessive daytime sleepiness that cannot otherwise be explained [6]. PLMS may present without any complaints of disturbed sleep or daytime sleepiness, especially in elderly subjects [7-9]. PLMS is relatively common in adults, but PLMD is rare. Recently, several studies have investigated the association between PLMS and sympathetic nervous system activation [10-14]. Furthermore, increased morbidity, cardiovascular diseases [15,16], and arrhythmia have been reported in patients with PLMS [17,18]. Although both PLMS and PLMA are related to disturbed sleep architecture, it is not clear how far their severity is affected by sleep disruption. In addition, there are limited data regarding the cutoff values of the PLMS and PLMA indices to cause disturbed sleep architecture. Hence, this study investigated the cutoff values of the PLMS and PLMA indices, which were associated with poorer sleep quality [20].

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MATERIALS AND METHODS

From May 2010 to September 2021, 8379 patients who visited the Fukuoka Urasoe Clinic underwent PSG with PLMS measurement. The chief complaint of the patients was daytime sleepiness and/or loud snoring. The PLMS was scored according to the American Academy of Sleep Medicine Criteria (2018) [21]. Patients with a total number of PLMS ≥ 15 per hour of sleep were defined as patients with PLMS. The 222 patients with PLMS were clinically diagnosed according to the diagnostic criteria of the International Classification of Sleep Disorders version 3 [6]. There were 54 patients with PLMD, 53 with primary snoring, 24 with narcolepsy, 23 with RBD, 22 with PLMS, 15 with insomnia, 12 with RLS, 8 with idiopathic hypersomnia, 2 with exploding head syndrome, 2 with sleep-related eating disorder, 2 with the sleep state misperception, 2 with insufficient sleep syndrome, 1 with bruxism, 1 with catathrenia, and 1 with leg myoclonus. Informed consent was obtained from all patients before enrollment in this study. The study protocol was approved by the Institutional Ethics Committee of Nakamura Clinic, Urasoe, Okinawa, Japan. The study was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments.

Polysomnography (PSG)

As described in our previous study, standard overnight PSG includes continuous monitoring using central Electroencephalography (EEG), electrooculography, submental and anterior tibial electromyography, and electrocardiography using conventional leads [22]. Airflow was monitored using oral and nasal thermistors, and respiratory effort was measured using respiratory inductance plethysmography with transducers placed around the chest and abdomen. Oxyhemoglobin saturation was continuously recorded using a pulse oximeter (3900P, Datex-Ohmeda Co., Louisville, CO, USA). All variables were continuously recorded using REMbrandt™ version 8.0 (Eebla, Broomfield, CO, USA) and RemLogic™ version 3.2 (Eebla, Thornton, CO, USA). All recordings were scored directly on the screen by a polysomnographer certified by the Japanese Society of Sleep Research. Apnea and hypopnea were scored according to the latest (2018) American Academy of Sleep Medicine Criteria [21]. We defined disturbed sleep architecture measured with PSG as having Sleep Efficiency (SE) < 85%, Total Sleep Time (TST) < 360 min, and percentage of Wake After Sleep Onset (WASO) in Sleep Period Time (SPT) ≥ 15% [23].

Statistical analyses

All statistical analyses were performed using 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). More precisely, it is a modified version of the R commander, designed to add statistical functions frequently used in biostatistics [24]. The t-test was used to compare the ages of the patients with and without impaired PSG variables. Fisher's exact test was used to compare the male composition between the patients with and without impaired PSG variables. Pearson's correlation test was used to analyze the association between the PLMS index and the continuous outcomes of sleep architecture, SE, TST, and WASO. Receiver Operating Characteristic (ROC) curve analysis was performed to identify the best cutoff values of PLMS and PLMA to predict impaired PSG variables. All continuous values are expressed as the mean ± standard deviation. Statistical significance was set at $P < 0.05$.

RESULTS

Participants

We included 222 patients aged > 18 years who scored ≥ 15 on the PLMS index and < 5 on the apnea-hypopnea index to exclude the effect of OSA. The clinical characteristics and sleep variables of the patients with PLMS ≥ 15 are shown in Table 1.

	Total (n=222)
Age (years)	55.1 ± 18.3
BMI (kg/m^2)	22.1 ± 3.25
Male, n (%)	108 (48.6%)
Female, n (%)	114 (51.4%)
AHI (number/h)	2.13 ± 1.42
Sleep time with SpO_2 < 90 % (%)	0.0503 ± 0.182
Lowest SpO_2 (%)	90.2 ± 7.73
Arousal index (number/h)	21.3 ± 15.0
PLMS index (number/h)	37.8 ± 24.9
PLMA index (number/h)	6.75 ± 9.65

TST (min)	349 ± 74.6
Sleep latency (min)	16.8 ± 24.8
SE (%)	77.2 ± 15.0
WASO (%)	21.0 ± 14.6
Stage N1 (%)	18.8 ± 12.5
Stage N2 (%)	57.5 ± 12.1
Stage N3 (%)	6.59 ± 7.99
Stage REM (%)	17.1 ± 6.56
Snore index (number/h)	76.5 ± 108

Note: PLMS index: Periodic Limb Movements in Sleep, BMI: Body Mass Index, AHI: Apnea-Hypopnea Index, PLMA index: Periodic Limb Movements in Sleep with Arousal, TST: Total Sleep Time, SE: Sleep Efficiency, WASO: Wake After Sleep Onset, REM: Rapid Eye Movement. Data are expressed as mean ± standard deviation or number (percentage).

Table 1: Clinical characteristics and sleep variables of the patients with PLMS ≥ 15.

Table 2 shows the results of the comparison of clinical variables between patients with PLMS with and without impaired PSG parameters. No significant difference was observed in male composition between patients with and without impaired PSG parameters (male with decreased SE: 50.3% vs. 45.6%, P = 0.575; male with decreased TST: 52.2% vs. 45.0%, P = 0.783; male with increased WASO: 50.0% vs. 46.9%, P = 0.590). However, the age value was higher in patients with PLMS with impaired PSG parameters compared with those without impaired PSG parameters (age value in decreased SE: 55.2 ± 16.8 vs. 37.6 ± 14.2, P < 0.001; age value in decreased TST: 55.8 ± 17.3 vs. 41.8 ± 15.9, P < 0.001; age value in increased WASO: 56.6 ± 16.7 vs. 38.8 ± 14.3, P < 0.001). Correlation analyses among the PLMS index, periodic limb movements in sleep with arousal index, sleep efficiency, total sleep time, and wake after sleep onset. Pearson correlation analysis showed that there was a significant correlation among SE, TST, and WASO for the PLMS index (PLMS index vs. SE: r = −0.368, P < 0.001; PLMS index vs. TST r = 0.368, P < 0.001; PLMS index vs. WASO: r = 0.381, P < 0.001) (Table 3). In addition, there was also a significant correlation among SE, TST, and WASO for the PLMA index (PLMA index vs. SE: r = −0.422, P<0.001; PLMA index vs. TST: r = −0.386, P < 0.001; PLMA index vs. WASO: r = 0.425, P < 0.001).

SE (%)	**Total (n=222)**	**Male, n** (%)	**P**	**Age (years)**	**P**
< 85	143	72 (50.3%)	0.58	37.6 ± 14.2	< 0.001
≥ 85	79	35 (45.6)		55.2 ± 16.9	
TST (min)	**Total (n=222)**	**Male, n** (%)	**P**	**Age (years)**	**P**
< 360	113	59 (52.2%)	0.78	55.8 ± 17.3	< 0.001
≥ 360	109	49 (45.0%)		41.8 ± 15.9	
WASO (%)	**Total (n=222)**	**Male, n** (%)	**P**	**Age (years)**	**P**
≥ 15	126	63 (50.0%)	0.59	56.6 ± 16.7	< 0.001
< 15	96	45 (46.9%)		38.8 ± 14.3	

Note: PSG: Polysomnography, SE: Sleep Efficency, TST: Total Sleep Time, WASO: Wake After Sleep Onset. Data are expressed as number (percentage) or mean ± standard deviation.

Table 2: Comparison of clinical variables between patients with PLMS with and without impaired PSG parameters.

	SE (%)		TST (min)		WASO (%)	
	r	P	r	P	r	P
PLMS index (number/h) 37.8 ± 24.9	-0.368	< 0.001	-0.638	< 0.001	0.381	< 0.001
PLMS index (number/h) 6.75 ± 9.65	-0.422	< 0.001	-0.386	< 0.001	0.425	< 0.001

Note: PLMS index: Periodic Limb Movements in Sleep with arousal Index, PSG: Polysomnography, SE: Sleep Efficency, TST: Total Sleep Time, WASO: Wake After Sleep Onset; Data are expressed as number (Percentage) or mean ± standard deviation or number.

Table 3: Correlation analysis among the PLMS index, PLMA index, SE, TST and WASO.

Receiver operating characteristic curve analyses

To clarify the threshold of the PLMS and PLMA indices in impaired PSG parameters, we performed ROC curve analysis. We used an SE of < 85%, a TST of < 360 min, and a percentage of WASO in the SPT ≥ 15% as the gold standard for evaluating impaired PSG parameters. ROC curve analysis showed that the diagnostic cutoff values of the PLMS index for decreased SE, decreased TST, and increased WASO were 28.8 (Area Under the Curve [AUC], 0.638; 95% confidence interval [CI], 0.563–0.714), 34.4 (AUC, 0.642; 95% CI, 0.569–0.715), and 34.5 (AUC, 0.646; 95% CI, 0.574–0.718), respectively (Table 4). ROC curve analysis showed that the diagnostic cutoff values of the PLMA index for decreased SE, decreased TST, and increased WASO were 4.00 (AUC, 0.632; 95% CI, 0.557–0.708), 5.16 (AUC, 0.612; 95% CI, 0.538-0.686), and 4.70 (AUC, 0.611; 95% CI, 0.537–0.685), respectively (Table 5).

DISCUSSION

The results of the present study revealed the cutoff values of the PLMS and PLMA indices to induce impaired PSG variables. Often, patients with PLMS do not complain of any symptoms, even if sleep quality is deceased [7-9]. The PLMS and PLMA indices can be used to predict impaired sleep quality.

In our study, both the PLMS and PLMA indices were significantly associated with impaired PSG parameters. However, the influence of PLMS and PLMA on sleep architecture measured using PSG is controversial. The PLMA index was associated with lower SE, but the PLMS index was not associated with lower SE in multivariate analysis of older men in the MrOS study [19]. In a study of Osteoporotic Fractures in older women, the PLMS index was not associated with decreased SE and TST, but the PLMA index was associated with decreased SE and TST [20]. The differences in number of patients and male composition

Gold standard	AUC	95% CI	Cutoff value	Sensitivity	Specificity
SE < 85 (%)	0.638	0.563-0.714	28.8	0.608	0.601
TST < 360 (min)	0.642	0.569-0.715	34.4	0.716	0.540
WASO ≥ 15 (%)	0.646	0.574-0.718	34.5	0.532	0.740

Note: ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidnce Interval; Data are expressed as number.

Table 4: ROC analysis of PLMS index (n=222).

Gold standard	AUC	95% CI	Cutoff value	Sensitivity	Specificity
SE < 85 (%)	0.632	0.557-0.708	4.00	0.658	0.608
TST < 360 (min)	0.612	0.538-0.686	5.16	0.697	0.513
WASO ≥ 15 (%)	0.611	0.537-0.685	4.70	0.524	0.688

Note: ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidnce Interval; Data are expressed as number.

Table 5: ROC analysis of PLMA index (n=222).

of the study may explain this discrepancy. In individuals in the SHIP-TREND study [5], PLMS index ≥ 15 was associated with higher WASO, lower TST, and lower SE compared with PLMS index < 15. This result was consistent with that of our study.

In our study, even if the PLMS index did not result in arousal, both the PLMS and PLMA indices affected the PSG parameters. It is easy to hypothesize that PLMA disturbs PSG parameters through fragmented sleep with arousal. Although we did not score autonomic arousal or perform spectral analyses on EEGs, there are several reports on the association between autonomic arousal and PLMS. Ferri et al. [25], reported that PLMS affects sleep architecture through autonomic arousal with heart rate modulation and increased delta and theta activity and progression to a higher frequency in spectral EEG analysis [1,25]. These factors may affect sleep stage shift and lead to disturbances in sleep architecture measured with PSG. In RLS, PLMS is reported to impair sleep by generating arousal instability, particularly during non-rapid eye movement sleep [26,27].

RLS often accompanies PLMS, and 12 patients with RLS who scored PLMS ≥ 15 were included in our study. Eisensehr et al. reported that the sleep architecture of RLS is different from that of PLMD without RLS symptoms, with more arousal not related to PLMS, and the ratio of PLMA to PLMS is decreased [28]. In our study, there were no differences in the number of arousals not related to PLMS and the ratio of PLMA to PLMS between the patients with RLS (N = 12) and those with PLMD (N = 54) (arousal number not related to PLMS: 27.9 ± 38.9 vs. 13.8 ± 7.32, P = 0.365; ratio of PLMA to PLMS: 0.321 ± 0.219 vs. 0.341 ± 0.263, P = 0.927). The effect of PLMS and PLMA on sleep quality in patients with PLMS with RLS may differ from that in patients without RLS. The cutoff values for impaired PSG parameters in patients with PLMS with RLS may also differ from those without RLS.

There is a sex difference in the effect of PLMS to sleep quality [19,20]. PLMS has a stronger effect on PSG parameters in older men than in older women. Hypothetically, the sleep architecture in older women is generally better than that in older men and that sleep in women is less sensitive to disturbances than that in men. In our study, differences in the impaired PSG variables (SE, TST, and WASO) in patients with PLMS between ages were observed, but not between sexes.

Age was higher in patients with impaired PSG parameters than in those without impaired PSG parameters (Table 2). To assess the effect of age, we divided the patients into age < 50 or ≥ 50 years and performed ROC analysis. AUC values in the ROC analysis for patients both aged < and ≥ 50 years were not superior to the AUC values in ROC analysis for all patients. However, the cutoff values for impaired PSG parameters differ depending on age. Further analysis is required to consider age when predicting impaired PSG parameters.

CONCLUSION

The results of the present study revealed cutoff values for PLMS and PLMA to predict impaired PSG variables. In the present study, both higher PLMS and PLMA indices were associated with impairment of SE, TST, and WASO. In addition, patients with PLMS index ≥ 28.8-34.5 or with PLMA index ≥ 4.00-5.16 independently had disturbed sleep architecture. To the best of our knowledge, this is the first study to demonstrate the cutoff values of the PLMS and PLMA indices to cause disturbed sleep architecture.

STUDY LIMITATIONS

The present study has some limitations. PSG does not correlate directly with sleep in the home environment and may poorly reflects actual sleep SE, TST, and WASO in a normal setting. The present data were from a single center; consequently, the present evidence may not be generalized. We did not assess the effects of age, sex, body mass index, medication, comorbidities, caffeine consumption, alcohol consumption, smoking, and physical activity, which may affect the PLMS index. We did not measure iron and magnesium levels in the blood chemistry and were not able to detect their influence on PLMS. We did not conduct a questionnaire test to investigate sleep-related complaints and did not assess the symptoms of PLMS. We defined impaired PSG parameters as SE < 85%, TST < 360 min, and percentage of WASO in SPT ≥ 15% because there are no established markers to evaluate sleep quality. The mechanisms underlying the effects of PLMS and PLMA on PSG parameters were not investigated in this study.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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