

# Different diagnostic criteria for periodic leg movements in patients with obstructive sleep apnea after continuous positive airway pressure titration

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Chih-Yu Huang<sup>1</sup>  
Chung-Chieh Yu<sup>1,2</sup>

<sup>1</sup>Division of Pulmonary, Critical Care, and Sleep Medicine, Chang Gung Memorial Hospital, Keelung, Taiwan, Republic of China; <sup>2</sup>College of Medicine, Chang Gung University, Taoyuan, Taiwan, Republic of China

**Objective:** Periodic leg movement in sleep (PLMS) is common among patients with obstructive sleep apnea (OSA). The PLMS frequency changes after continuous positive airway pressure (CPAP) titration. This study investigated the effects of two PLMS diagnostic criteria on PLMS prevalence and the restless leg syndrome (RLS) detection rate in patients with OSA before and after CPAP titration.

**Methods:** This retrospective study included patients with OSA who received polysomnography (PSG) and successful CPAP titration from December 2012 to December 2014. Their clinical variables and sleep parameters were evaluated using the PLMS diagnostic criteria: PLMS index (PLMI)  $\geq 5$  and  $\geq 15$ . PLMS prevalence and the RLS detection rate were analyzed according to the PLMI before and after CPAP.

**Results:** In patients with OSA with a PLMI of  $\geq 5$  and  $\geq 15$  after PSG with CPAP titration, the PLMS prevalence was 20.1% (76/378) and 4.5% (17/378), respectively, which revealed CPAP titration increased PLMI. Moreover, in terms of PLMI  $\geq 5$  and  $\geq 15$ , PSG with CPAP titration led to significantly higher PLMS prevalence than PSG alone (20.1% vs 7.1% and 4.5% vs 0.8%, respectively; both  $P < 0.001$ ). PLMI  $\geq 5$  also demonstrated a higher RLS detection rate than PLMI  $\geq 15$  did (69.2% vs 15.4%;  $P = 0.016$ ).

**Conclusion:** In patients with OSA, CPAP titration increases PLMS prevalence and the PLMI regardless of whether PLMI is  $\geq 5$  or  $\geq 15$ . The use of the current diagnostic criteria, PLMI  $\geq 15$ , for PLMS may lead to underestimation of PLMS prevalence and the RLS detection rate in patients with OSA.

**Keywords:** continuous positive airway pressure, obstructive sleep apnea, periodic leg movements in sleep, polysomnography, restless leg syndrome

## Introduction

Periodic leg movement in sleep (PLMS) involves repetitive leg movement at night, which is recorded through polysomnography (PSG). Periodic leg movement (PLM) consists of  $\geq 4$  consecutive events of 0.5–10-second-long stereotypical leg movements (LMs) occurring at a 5–90-second interval in sleep.<sup>1</sup> Periodic limb movement disorder (PLMD) is characterized by the presence of PLMS accompanied by insomnia. PLMD may also be associated with daytime hypersomnia or unrefreshing sleep after the exclusion of other sleep disorders.<sup>2</sup> PLMS is frequently present in patients with restless legs syndrome (RLS). A study found that more than 80% of patients with RLS had PLMS.<sup>3</sup> The International Restless Legs Syndrome Study Group (IRLSSG) reported that PLMS is a supportive criterion for RLS diagnosis.<sup>4</sup>

Correspondence: Chung-Chieh Yu  
Division of Pulmonary, Critical Care, and Sleep Medicine, Chang Gung Memorial Hospital, 222, Maijin Road, Keelung 204, Taiwan, Republic of China  
Tel +886 22 431 3131 ext. 3168  
Fax +886 22 433 5342  
Email terminatorchieh@yahoo.com.tw

Before 2005, a PLMS index (PLMI) of  $\geq 5$  was considered clinically significant.<sup>5</sup> According to this criterion, studies reported that PLMS prevalence was 4–11% in adults<sup>6</sup> and the PLMS prevalence increased with age.<sup>7</sup> In 2005, the American Academy of Sleep Medicine (AASM) established the current PLMI cut-off of  $\geq 15$  as the PLMD criterion.<sup>8</sup> However, clinically, the differences in the PLMS diagnostic criteria used may influence PLMS prevalence and the RLS detection rate.

In PSG studies, PLMS is usually concurrently noted with obstructive sleep apnea (OSA). Moreover, patients with sleep-disordered breathing may present with RLS. However, very few studies have examined PLMS prevalence and RLS detection rate in patients with OSA. A retrospective study in Canada reported PLMS in 48% of patients with OSA.<sup>9</sup> Moreover, a small prospective study found that RLS occurred in 8.3% of patients with OSA in the United States.<sup>10</sup> The occurrence and clinical relevance of patients with OSA coexisting with PLMS remain unclear.

Continuous positive airway pressure (CPAP) is the most effective therapy for OSA. Some studies have noted that administering CPAP therapy to patients with OSA may increase PLMS prevalence.<sup>11</sup> Studies also indicate that the presence of PLMS represents persistent sleep-disordered breathing.<sup>12</sup> By contrast, another investigation reported a decrease in the PLMI after CPAP therapy.<sup>13</sup> Recent studies have suggested that OSA masks post-CPAP titration PLMS.<sup>14,15</sup> Thus, PLMS prevalence and frequency in relation to CPAP titration in patients with OSA remains unclear.

The main purpose of this study was to evaluate two PLMS diagnostic criteria and their effects on PLMS prevalence and the RLS detection rate in patients with OSA before and after CPAP titration.

## Methods

### Participants

This retrospective study included 443 patients with an apnea–hypopnea index (AHI) of  $\geq 5$ . The patients underwent both baseline PSG and a second-night PSG for manual CPAP titration between December 2012 and December 2014. The patients were excluded if CPAP titration failed. Patients were also excluded if they used dopaminergic agents or antidepressants, which could affect PLMS before baseline PSG. Before data review, this study was approved by The Institutional Review Board of Chang Gung Memorial Hospital (IRB/CGMH No. 201600860B0) and the informed consent to review

their medical records was not required. Patient confidentiality was maintained as no patients' identifiers were collected and the private will be carefully protected. All research process was in accordance with the Declaration of Helsinki.

The age, gender, body mass index (BMI), neck circumference (NC), and medical history of the patients were recorded. Detailed sleep parameters were measured, including the total sleep time (TST), sleep efficiency, slow wave sleep (SWS) and rapid-eye movement (REM) percentages, mean and minimal oxyhemoglobin saturation, and mean desaturation. The daytime sleepiness severity was measured on the Epworth Sleepiness Scale (ESS).<sup>16</sup> RLS was diagnosed according to the five clinical criteria defined by the IRLSSG in 2014.<sup>17</sup>

### PSG and CPAP titration

Standard overnight PSG was performed using a computerized PSG system (N7000 Embla, Broomfield, USA). The recorded parameters were as follows: electroencephalograms (EEGs), bilateral electrooculograms (EOGs), submental and bilateral anterior tibialis electromyograms (EMGs), electrocardiograms (ECGs), the nasal and oronasal airflow (by using nasal pressure monitor and thermistor), arterial oxygen saturation (through finger probe pulse oximetry), chest and abdominal movements (through inductance plethysmography), body position, and sound intensity. Sleep stages were scored manually in 30-second epochs by using the AASM scoring criteria.<sup>18</sup> CPAP titration was administered using AutoSet Spirit S8 (ResMed, Sydney, Australia) in the sleep laboratory on a separate night. In the CPAP titration study, manual CPAP titration was performed to determine an optimal CPAP level.<sup>19</sup> The optimal CPAP level was defined as the lowest effective pressure to eliminate most respiratory events, including apnea, hypopnea, and snoring in all body positions and all sleep stages, particularly in the supine position and REM sleep, respectively.

### Scoring

Obstructive apnea was defined as the absence of airflow for at least 10 seconds in the presence of respiratory effort, whereas central apnea was defined as the absence of airflow without concurrent respiratory effort. Hypopnea was considered when more than a 50% decrease in airflow occurred for more than 10 seconds, followed by at least 3% oxygen desaturation or EEG arousal.<sup>18</sup> The AHI was defined as the average number of apneas and hypopneas per hour of sleep. LM caused an 8- $\mu$ V increase in the EMG voltage of the right and left anterior tibialis above the resting EMG voltage. The increase lasted

0.5–10 seconds. LM with EEG arousal was also calculated during sleep, which allowed a LM arousal index (LMAI) to be generated. LMs occurring in a wide time window from 0.5 seconds before the start of a respiratory event (apnea or hypopnea) until 0.5 seconds after its end were not counted. PLM was defined as a minimum of four consecutive LM events with a 5–90-second interval during sleep. The PLMI was scored as the number of PLM per hour of TST.<sup>20</sup> Two PLMS diagnostic criteria with a PLMI of  $\geq 5$ <sup>3,5</sup> and  $\geq 15$ <sup>2</sup> were assessed. The RLS detection rate was defined as the percentage of patients with RLS matching the PLMS diagnostic criteria divided by the total number of patients with RLS who were diagnosed using the clinical criteria.

## Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). The patient characteristics after using the PLMS diagnostic criteria (PLMI  $\geq 5$  and  $\geq 15$ ) are presented as a mean  $\pm$  standard deviation or number (%). The Wilcoxon signed-rank tests were used to compare the sleep parameters, AHI, and PLMI of the patients at baseline and after CPAP titration. Pearson's correlation coefficient was used to evaluate the relationship between PLMI and AHI before CPAP titration and the relationship between the increase of PLMI and the decrease of AHI after CPAP titration. McNemar's test was used to evaluate the differences in PLMS prevalence and the RLS detection rate after using PLMI  $\geq 5$  or 15 with PSG alone and PSG with CPAP titration. The variables associated with PLMS were evaluated through multivariate logistic regression by using PLMI  $\geq 5$  and 15. A *P*-value of  $<0.05$  was considered statistically significant.

## Results

### Subject description

After the exclusion of 20 patients with failed CPAP titration and 45 patients with dopaminergic agent or antidepressant use, 378 patients with OSA were finally included in this study. The patients that met the PLMS diagnostic criterion of PLMI  $\geq 5$  or  $\geq 15$  at both PSG with and without CPAP titration were considered to have PLMS one time. Among the patients with PLMI  $\geq 5$ , 27 (7.1%) had PLMS after PSG alone and 76 (20.1%) had PLMS after PSG with CPAP titration. Among the patients with PLMI  $\geq 15$ , three (0.8%) had PLMS after PSG alone and 17 (4.5%) had PLMS after PSG with CPAP titration (Figure 1). The basic patient

characteristics, including the age, gender, BMI, ESS, NC, AHI, RLS, and past history are listed in Table 1. The mean age of the participants was 49.5 years, with a mean BMI of 28.5 kg/m<sup>2</sup>, and 83.1% of the patients were male.

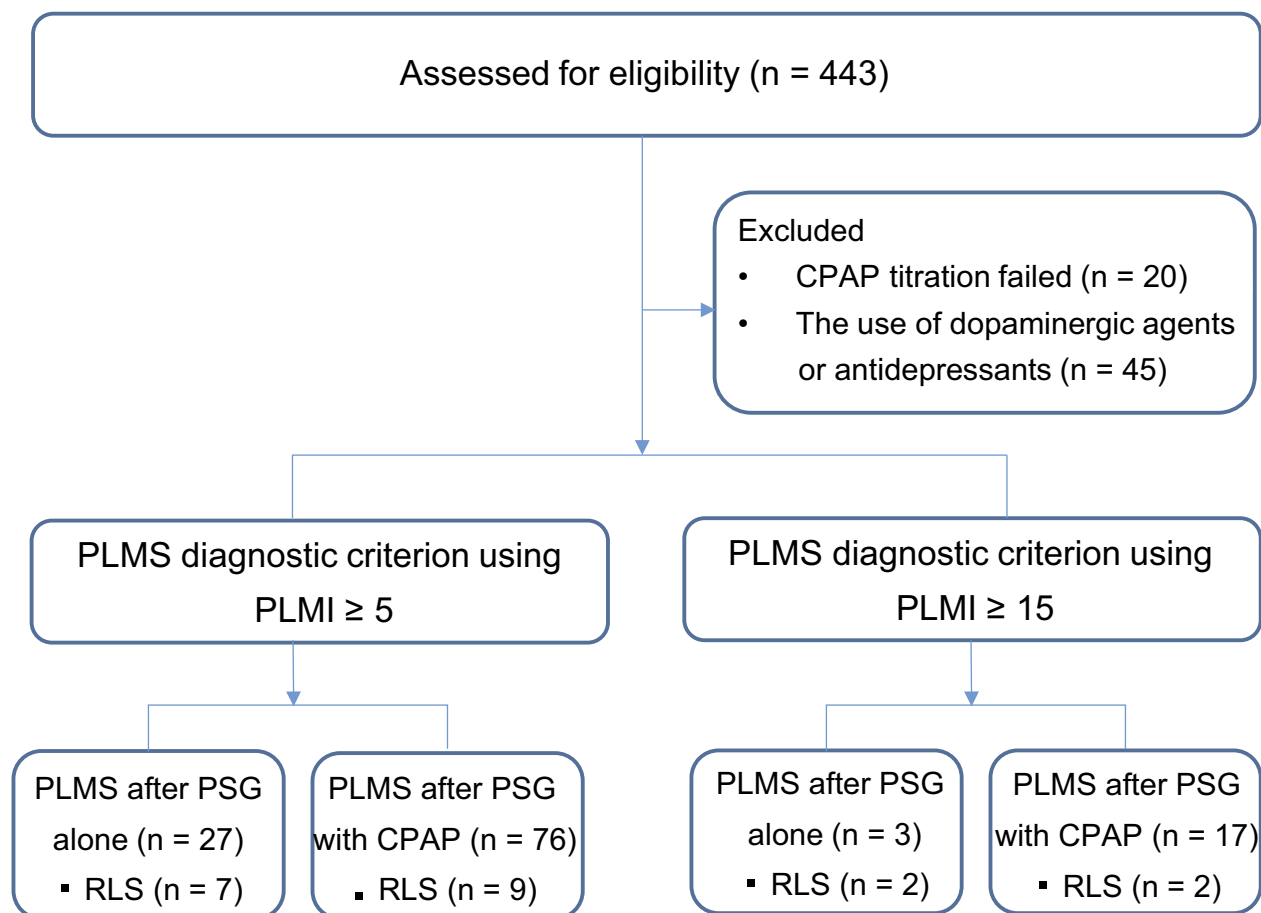
### PLMI and sleep parameters after PSG with CPAP titration

In patients with PLMI  $\geq 5$ , the PLMI increased in 60 (78.9%) patients and decreased in the others (*n*=16, 21.1%) after CPAP titration. In patients with PLMI  $\geq 15$ , the PLMI increased in 15 (88.2%) patients and decreased in the others (*n*=2, 11.8%) after CPAP titration. The PLMI, AHI, and sleep parameters of the patients with PLMI  $\geq 5$  and  $\geq 15$  after PSG with CPAP titration are listed in Table 2. CPAP titration significantly improved nocturnal desaturation and sleep architecture. The TST, SWS, and REM sleep of both the groups increased. Among patients with PLMI  $\geq 5$  and  $\geq 15$ , compared with baseline PSG, CPAP titration reduced AHI (5.92 $\pm$ 4.45 vs 55.68 $\pm$ 25.26 and 4.61 $\pm$ 3.00 vs 53.02 $\pm$ 25.42, respectively; both *P*<0.001) and increased PLMI (10.09 $\pm$ 6.98 vs 4.08 $\pm$ 4.91, *P*<0.001 and 19.67 $\pm$ 7.70 vs 5.96 $\pm$ 6.59, *P*=0.002, respectively). PLMI (*r*=−0.611, *P*<0.001) was negatively correlated with AHI before CPAP and the increase of PLMI (*r*=0.426, *P*<0.001) was positively correlated with the decrease of AHI from baseline PSG to CPAP titration among OSA patients coexisting with PLMS.

### PLMS prevalence and the RLS detection rate

PLMS prevalence using PLMI  $\geq 5$  or  $\geq 15$  after PSG alone and PSG with CPAP titration is listed in Table 3. PLMS prevalence after PSG with CPAP titration was significantly higher than that after PSG alone irrespective of the diagnostic criteria (PLMI  $\geq 5$ : 20.1% vs 7.1%; PLMI  $\geq 15$ : 4.5% vs 0.8%; both *P*<0.001). Moreover, different PLMS diagnostic criteria significantly affected PLMS prevalence both after PSG alone and PSG with CPAP titration.

The RLS detection rate was also influenced by the PLMS diagnostic criteria (Table 4). In total, 13 patients were diagnosed as having RLS according to the IRLSSG diagnostic criteria. Of them, seven (53.8%) and two (15.4%) had a PLMI of  $\geq 5$  and  $\geq 15$  after PSG alone, respectively; however, the results were not significant. By contrast, nine (69.2%) and two (15.4%) patients had a PLMI of  $\geq 5$  and  $\geq 15$  after PSG with CPAP titration, respectively, and the results were significant.



**Figure 1** Study flow. In this study, 443 patients with an AHI of  $\geq 5$  were enrolled. These patients underwent both baseline PSG and a second-night PSG for manual CPAP titration. Among the 443 patients, 20 and 45 were excluded because of CPAP titration failure and dopaminergic agent or antidepressant use, respectively. Finally, 378 patients were included in this study. Patients with a PLMI of  $\geq 5$  or  $\geq 15$  after PSG with CPAP titration were considered to have PLMS one time. Among the patients with PLMS, 27 (7.1%) and 76 (20.1%) had a PLMI of  $\geq 5$  after PSG alone and PSG with CPAP titration, respectively, whereas only three (0.8%) and 17 (4.5%) had a PLMI of  $\geq 15$  after PSG alone and PSG with CPAP titration, respectively.

**Abbreviations:** AHI, apnea-hypopnea index; PSG, polysomnography; CPAP, continuous positive airway pressure; PLMI, periodic leg movement in sleep index; PLMS, periodic leg movement in sleep.

## Factors associated with PLMS

The results of the multivariate logistic regression of the factors associated with PLMS after using the two diagnostic criteria (PLMI  $\geq 5$  and  $\geq 15$ ) are presented in Table 5. For PLMI  $\geq 5$ , RLS (OR: 15.101, 95% CI: 3.965–57.515;  $P < 0.001$ ) and chronic kidney disease (OR: 3.633, 95% CI: 1.084–12.172;  $P = 0.037$ ) were independently associated with PLMS; however, no variables were associated with PLMS for PLMI  $\geq 15$ .

## Discussion

In a sample of consecutive patients with OSA, different PLMS diagnostic criteria and CPAP application had a significant influence on PLMS prevalence and the RLS

detection rate. The PLMS prevalence and frequency were higher when PSG was combined with CPAP titration compared with when PSG was used alone. PLMS prevalence and the RLS detection rate were higher when the PLMI was  $\geq 5$  than when the PLMI was  $\geq 15$ .

PLMS appears to be more common in patients with OSA than in the general population. PLMS prevalence in OSA patients with a PLMI of  $\geq 5$  was 48% in Canada<sup>9</sup> and 33% in the United States.<sup>21</sup> However, very few studies have examined PLMS prevalence in Asian patients with OSA. In our study, 20.1% of patients with OSA had PLMS with a PLMI of  $\geq 5$ . These data reveal a lower PLMS prevalence in patients with OSA in Taiwan than in Western countries. By using the PLMS diagnostic criterion of PLMI  $\geq 15$ , Ren et al reported that PLMS prevalence

**Table 1** Patient characteristics stratified according to the PLMS diagnostic criteria (PLMI  $\geq 5$  and  $\geq 15$ ) after PSG with CPAP titration

Characteristics	Total (n=378)	PLMI $\geq 5$ (n=76)	PLMI $\geq 15$ (n=17)
Age (years)	49.53 $\pm$ 12.57	51.61 $\pm$ 13.20	52.65 $\pm$ 12.05
Male	314 (83.1)	61 (80.3)	11 (64.7)
BMI (kg/m <sup>2</sup> )	28.49 $\pm$ 4.75	29.02 $\pm$ 4.83	29.23 $\pm$ 5.12
ESS	10.40 $\pm$ 4.50	10.91 $\pm$ 4.09	9.00 $\pm$ 3.74
NC (cm)	39.74 $\pm$ 3.61	40.16 $\pm$ 4.16	39.71 $\pm$ 4.07
AHI (events/h)	51.95 $\pm$ 22.04	55.68 $\pm$ 25.26	53.02 $\pm$ 25.42
RLS	13 (3.4)	9 (11.8)	2 (11.8)
Past history			
CKD	14 (3.7)	8 (10.1)	3 (17.6)
Hypertension	162 (42.9)	44 (57.9)	11 (64.7)
DM	54 (14.3)	13 (17.1)	5 (29.4)
CVA	12 (3.2)	3 (3.9)	0 (0.0)
Heart failure	10 (2.6)	5 (6.6)	1 (5.9)

**Notes:** Data are presented as mean  $\pm$  SD or number (%).

**Abbreviations:** PLMS, periodic leg movements in sleep; PLMI, periodic leg movement index; PSG, polysomnography; CPAP, continuous positive airway pressure; BMI, body mass index; ESS, Epworth Sleepiness Scale; NC, neck circumference; AHI, apnea-hypopnea index; RLS, restless leg syndrome; CKD, chronic kidney disease; DM, diabetes mellitus; CVA, cerebrovascular accident.

**Table 2** Sleep parameters of patients with a PLMI of  $\geq 5$  (n=76) and  $\geq 15$  (n=17) after PSG with CPAP titration

	PLMI $\geq 5$			PLMI $\geq 15$		
	Baseline PSG	CPAP titration	P	Baseline PSG	CPAP titration	P
TST (minutes)	285.20 $\pm$ 60.38	309.61 $\pm$ 53.94	0.004*	271.79 $\pm$ 64.49	316.79 $\pm$ 56.66	0.033*
SE (% of TST)	74.41 $\pm$ 15.27	81.05 $\pm$ 13.89	0.001*	69.88 $\pm$ 15.99	81.78 $\pm$ 13.66	0.055
Stage SWS (% of TST)	14.92 $\pm$ 11.44	23.75 $\pm$ 12.40	<0.001*	16.92 $\pm$ 13.41	28.65 $\pm$ 13.87	0.003*
Stage REM (% of TST)	13.59 $\pm$ 8.48	19.95 $\pm$ 9.49	<0.001*	10.22 $\pm$ 8.48	18.54 $\pm$ 7.04	0.006*
AHI (events/h)	55.68 $\pm$ 25.26	5.92 $\pm$ 4.45	<0.001*	53.02 $\pm$ 25.42	4.61 $\pm$ 3.00	<0.001*
Mean SaO <sub>2</sub> (%)	91.68 $\pm$ 3.87	94.21 $\pm$ 1.83	<0.001*	92.56 $\pm$ 2.06	94.31 $\pm$ 1.16	0.001*
Minimal SaO <sub>2</sub> (%)	72.26 $\pm$ 12.14	84.21 $\pm$ 11.04	<0.001*	71.88 $\pm$ 11.95	85.00 $\pm$ 6.45	0.001*
Mean desaturation (%)	8.46 $\pm$ 4.74	4.28 $\pm$ 1.42	<0.001*	7.54 $\pm$ 3.49	4.08 $\pm$ 1.47	0.001*
PLMI (events/h)	4.08 $\pm$ 4.91	10.09 $\pm$ 6.98	<0.001*	5.96 $\pm$ 6.59	19.67 $\pm$ 7.70	0.002*
LMAI (events/h)	1.18 $\pm$ 1.81	3.64 $\pm$ 4.60	<0.001*	1.21 $\pm$ 2.00	6.27 $\pm$ 7.64	0.006*

**Note:** Data are presented as mean  $\pm$  SD. \*Significant at  $P < 0.05$ .

**Abbreviations:** PLMI, periodic leg movement index; PSG, polysomnography; CPAP, continuous positive airway pressure; TST, total sleep time; SE, sleep efficiency; SWS, slow wave sleep; REM, rapid eye movement; AHI, apnea-hypopnea index; SaO<sub>2</sub>, oxyhemoglobin saturation; LMAI, leg movement arousal index.

**Table 3** PLMS prevalence stratified according to the PLMS diagnostic criteria (PLMI  $\geq 5$  and  $\geq 15$ ) after PSG alone and PSG with CPAP titration

Different criteria	PLMI $\geq 5$	PLMI $\geq 15$	P
PLMS after PSG alone	27 (7.1)	3 (0.8)	<0.001*
PLMS after PSG with CPAP titration	76 (20.1)	17 (4.5)	<0.001*
P	<0.001*	<0.001*	

**Note:** Data are presented as number (%). \*Significant at  $P < 0.05$ .

**Abbreviations:** PLMS, periodic leg movements in sleep; PLMI, periodic leg movement index; PSG, polysomnography; CPAP, continuous positive airway pressure.

was 20.1% in a sample of 364 patients with OSA in China.<sup>22</sup> In our study, PLMS prevalence in patients with a PLMI of  $\geq 15$  was 4.5% lower than the values reported by Ren et al. However, we could not clearly elucidate the

reason for this relatively low PLMS prevalence. In a Japanese study, among patients with PLMI  $\geq 15$ , women had a higher PLMS prevalence than men.<sup>23</sup> Our study had a higher men/women ratio (4.9/1) than did the study of



**Table 4** The RLS detection rate stratified according to the PLMS diagnostic criteria (PLMI  $\geq 5$  and  $\geq 15$ ) after PSG alone and PSG with CPAP titration

Different criteria	PLMI $\geq 5$	PLMI $\geq 15$	P
RLS after PSG alone	7 (53.8)	2 (15.4)	0.063
RLS after PSG with CPAP titration	9 (69.2)	2 (15.4)	0.016*

**Note:** Data are presented as number (%). \*Significant at  $P < 0.05$ .

**Abbreviations:** RLS, restless leg syndrome; PLMS, periodic leg movements in sleep; PLMI, periodic leg movement index; PSG, polysomnography; CPAP, continuous positive airway pressure.

**Table 5** Multivariate analyses of the PLMS associated characteristics for PLMI  $\geq 5$  and  $\geq 15$ 

Variables	PLMI $\geq 5$			PLMI $\geq 15$		
	OR	95% CI	P	OR	95% CI	P
Age	1.005	0.981–1.031	0.671	1.004	0.956–1.055	0.866
Male	0.570	0.255–1.276	0.171	0.293	0.079–1.087	0.066
BMI	1.000	0.922–1.085	0.993	1.031	0.897–1.185	0.668
ESS	1.039	0.978–1.103	0.217	0.931	0.829–1.045	0.225
AHI	1.012	0.998–1.025	0.086	1.005	0.980–1.030	0.700
RLS	15.101	3.965–57.515	$<0.001^*$	4.656	0.739–29.337	0.101
CKD	3.633	1.084–12.172	0.037*	4.329	0.905–20.703	0.067
Hypertension	1.749	0.975–3.139	0.061	1.902	0.621–5.823	0.260
Heart failure	2.992	0.742–12.063	0.123	1.182	0.114–12.305	0.889

**Note:** \*Significant at  $P < 0.05$ .

**Abbreviations:** PLMS, periodic leg movements in sleep; PLMI, periodic leg movement index; BMI, body mass index; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; RLS, restless leg syndrome; CKD, chronic kidney disease.

Ren et al (men/women =1/1). Therefore, different gender ratios may have led to the relatively low PLMS prevalence in our study.

A large multinational study that included 15,391 adults from the United States and five European countries reported the RLS prevalence was 7.2% in the general population.<sup>24</sup> However, the RLS prevalence in the Taiwanese population (1.57%) has been reported to be much lower than that in Caucasians due to genetic differences.<sup>25</sup> Our study revealed a higher RLS prevalence (3.4%) in patients with OSA than in the general population in Taiwan. Moreover, clinicians consider that PLMS occurrence is likely associated with RLS after the exclusion of other precipitating factors because PLMS is noted in most patients with RLS. In our study, we examined the RLS detection rate in PLMS patients by using two criteria and found that only two out of 13 patients with RLS had a PLMI of  $\geq 15$ , whereas nine out of 13 patients with RLS had a PLMI of  $\geq 5$ . Moreover, RLS was an independent factor when the PLMS diagnostic criterion of PLMI  $\geq 5$  was used, whereas no such relationship was seen for PLMI  $\geq 15$ . Although RLS should be diagnosed with clinical criteria, using the diagnostic criterion of PLMI  $\geq 15$  in clinical practice can influence the RLS detection rate. Various specialists

arrange PSG for different sleep disorders and they may not routinely evaluate RLS symptoms that would miss RLS diagnosis. In our study, PLMI  $\geq 5$  demonstrated a higher RLS detection rate than PLMI  $\geq 15$  (69.2% vs 15.4%). If PLMS is discovered through PSG with CPAP titration, it will remind the clinician to check clinical symptoms and increase the RLS detection rate. Therefore, our study want to illustrate the PLMI  $\geq 5$  or  $\geq 15$ , CPAP titration, and routinely evaluate RLS symptoms are important factors to affect the detection rate of PLMS and RLS.

Numerous studies have discussed the etiology of the change in PLMI from baseline PSG to CPAP titration, and various theories have been proposed. A 1989 study indicated that CPAP therapy can worsen PLMS.<sup>11</sup> Subsequent studies have found that the influence of CPAP on PLMI may be related to the score unmasking PLMS when respiratory events are adequately controlled by CPAP.<sup>14,15</sup> By contrast, Yamashiro and Kryger reported that PLMI decreased after CPAP titration.<sup>13</sup> A recent investigation hypothesized that CPAP therapy improves residual respiratory-effort related arousals, which may lead to decreased PLMI.<sup>14</sup> In our study, only small proportion of patients were decreased PLMI and high proportional patients were increased PLMI

after CPAP titration. It means that the mechanism of the score unmasking PLMS and CPAP therapy improves residual respiratory-effort related arousals are existence in different type of OSA patients. Nevertheless, the PLMI increased from the baseline PSG to CPAP titration with a reduction in AHI in patients with both OSA and PLMS regardless of PLMI  $\geq 5$  or  $\geq 15$ . A negative correlation was demonstrated between PLMI and AHI before CPAP titration and a positive correlation was demonstrated between the increase of PLMI and the decrease of AHI after CPAP titration. Those data support that the mechanism of the score unmasking PLMS seems play more important role. These findings are consistent with that of Hedli et al,<sup>15</sup> which indicates that respiratory events may mask PLMS, which appears with CPAP therapy. Furthermore, the current AASM scoring criteria emphasize that PLM should only be counted if the PLM is spontaneous and not caused by respiratory events.<sup>20</sup> Thus, LM events occurring within 0.5 seconds of apnea or hypopnea are considered as respiratory-related LMs and deleted during manual scoring. PLMS prevalence in patients with OSA may be underestimated in baseline PSG. The real presentation of PLMS should occur after a treatment for OSA, such as CPAP, is implemented.

The recognition and distribution of true PLMS and respiratory event-associated LMs in patients with OSA have been debated considerably. Recent studies have suggested that the elimination of all LMs associated with respiratory events is possibly an incorrect practice because the distribution of respiratory-related LMs increases mainly over an interval of  $-2$  to  $10.25$  seconds around the end of respiratory events.<sup>26,27</sup> Manconi et al reported that respiratory-related LMs were not augmented at the beginning or middle of respiratory events but clustered only around the end of respiratory events.<sup>28</sup> These findings suggest that the duration and distribution of respiratory-related LMs are different compared with the AASM criteria for scoring LMs. After the application of the AASM criteria, many cases of PLMS can be eliminated from the counts that have not been eliminated under CPAP therapy because of the disappearance of most respiratory events.

The analysis of hypersomnia symptoms indicated that ESS was not an independent factor associated with PLMS occurrence based on either PLMI  $\geq 5$  or  $\geq 15$  as the PLMS diagnostic criterion in patients with OSA. Chervin et al and Haba-Rubio et al have also reported that concurrent OSA and PLMS are not associated with increased hypersomnia.<sup>29,30</sup> We propose that PLMS is not treated even if the PLMI increases after CPAP therapy without

any clinical symptoms. Further investigation is required for confirming whether concurrent PLMS and OSA results in additive consequences, such as cardiovascular events.

This study has certain limitations. First, we did not investigate PLMD. The diagnosis of PLMD requires the exclusion of other sleep disorders. However, all these sleep disorders cannot be identified through a simple chart review. Thus, we did not include PLMD in this study. Second, this study was a retrospective one and we did not obtain follow-up data after long-term CPAP therapy. Additional prospective studies are required to assess the effect of long-term CPAP on PLMS in patients with OSA. Third, the common medical or behavioral condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping) can be mistaken for RLS. A retrospective study with chart review may not exclude RLS-mimics completely.

## Conclusion

CPAP titration increases the prevalence of PLMS, which suggests that OSA masks PLMS. PLMS prevalence and the RLS detection rate were higher when the PLMI was  $\geq 5$  than when the PLMI was  $\geq 15$ . Therefore, the current AASM criteria for scoring LMs and the PLMS diagnostic criterion with PLMI  $\geq 15$  require reconsideration.

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## Disclosure

The authors report no conflicts of interest in this work.

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