Positional obstructive sleep apnea and periodic limb movement during sleep: A large multicenter study

Sleep apnea and periodic limb movements

Jae Hyun Soh, M.D.^{1†}, Yun Jin Kang, M.D., Ph.D.^{2†}, Won-Hyuck Yoon, M.S.³, Chan-Soon Park,

M.D., Ph.D.^{4*}, Hyun-Woo Shin, M.D., Ph.D.^{3,5,6,7,8,9*}

¹Seoul National University College of Medicine, Seoul, Korea.

²Department of Otorhinolaryngology-Head and Neck Surgery, Soonchunhyang University College of Medicine, Cheonan, Korea.

³OUaR LaB, Inc., Seoul, Korea.

⁴Department of Otorhinolaryngology-Head and Neck Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea.

⁵Department of Pharmacology, Seoul National University College of Medicine, Seoul, Korea.

⁶Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea.

⁷Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea.

⁸Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul, Korea.

⁹Sensory Organ Research Institute, Seoul National University College of Medicine, Seoul, Korea.

[†]Jae Hyun Soh and [†]Yun Jin Kang equally contributed to this work as the first author

*Corresponding author:

Chan-Soon Park, M.D., Ph.D.

Department of Otorhinolaryngology-Head and Neck Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea Phone: +82-31-249-8968, Fax: +82-31-257-3752, E-mail: pcs0112@catholic.ac.kr

Hyun-Woo Shin, M.D., Ph.D.

Department of Pharmacology, Seoul National University College of Medicine and Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, 103 Daehak-ro, Jongno-gu, Seoul (03080), Korea

Phone: +82-2-740-8285; Fax: +82-2-745-7996; E-mail: charlie@snu.ac.kr

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ORCiD:

Jae Hyun Soh: 0009-0000-9245-0815 Yun Jin Kang: 0000-0002-7677-4219 Won-Hyuck Yoon: 0000-0001-7942-4196 Chan-Soon Park: 0000-0003-3692-3344 Hyun-Woo Shin: 0000-0002-4038-9992

Author contributions:

Conceptualization, H.-W.S.; methodology, J.H.S., W.-H.Y., H.-W. S.; software, J.H.S., W.-H.Y.; validation, Y.J.K.; formal analysis, Y.J.K., W.-H.Y.; resources, H.-W.S.; data curation, J.H.S., W.-H.Y.; writing—original draft preparation and writing—review and editing, J.H.S., Y.J.K., C.-S.P., H.-W.S.; supervision, C.-S.P., H.-W.S.; project administration, C.-S.P., H.-W.S.; and funding acquisition, H.-W.S., Y.J.K. All authors have read and agreed to the published version of the manuscript.

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Highlights

- We examined the relationship between positional obstructive sleep apnea, obstructive sleep apnea (OSA), and periodic limb movement during sleep with OSA severity.
- We retrospectively reviewed 6,140 diagnostic polysomnography raw data from multi-center data base with event-syncronized analysis.
- Positional obstructive sleep apnea may increase periodic limb movement during sleep prevalence, particularly in severe OSA patients.
- If periodic limb movement during sleep is suspected, it is critical to investigate positional obstructive sleep apnea status and determine OSA severity.

5

Abstract

Objectives: The relationships among positional obstructive sleep apnea (POSA), obstructive sleep apnea (OSA), and periodic limb movement during sleep (PLMS) are unclear. We analyzed these relationships according to OSA severity and explored the underlying mechanisms.

Methods: We retrospectively reviewed 6,140 eligible participants who underwent full-night diagnostic polysomnography in four clinical centers over a period of 5 years with event-synchronized analysis. The PLMS index (PLMI) and periodic limb movements with arousal index (PLMAI) were evaluated. The effects of POSA on the PLMI, PLMAI, and PLMS were analyzed according to OSA severity.

Results: The mean PLMI and PLMAI, as well as PLMS prevalence, were significantly lower in those with severe OSA than in those with mild and moderate OSA. The mean PLMI was higher in mild OSA group than in control group. The mean PLMI (4.80 ± 12.71 vs. 2.59 ± 9.82 events/h, p < 0.001) and PLMAI (0.89 ± 3.66 vs. 0.53 ± 3.33 events/h, p < 0.001), and the prevalence of PLMS (11% vs. 5.3%, p < 0.001) were higher in patients with POSA than patients with non-POSA. This trend was particularly marked in severe OSA group (OR 1.55, 95%CI [1.07-2.27]) and less so in mild (OR 0.56, 95%CI [0.30-1.03]) and moderate (OR 1.82, 95%CI [0.99-3.34]) OSA groups.

Conclusion: The POSA group tended to have a higher prevalence of PLMS, particularly in those with severe OSA. If PLMS is prominent, diagnosis and treatment of POSA and OSA may be considered.

Keywords: Sleep apnea, Obstructive; Sleep Apnea Syndromes; Periodic Limb Movement Disorder; Sleep-Related Periodic Leg Movements, Excessive; Supine Position

Introduction

Periodic limb movement during sleep (PLMS) is characterized by periodic episodes of repetitive, highly stereotyped involuntary movements of the lower extremities [1] that may be associated with arousal. Thus, although not generally associated with insomnia, PLMS causes fragmented sleep and excessive daytime sleepiness [1, 2]. PLMS is observed in patients with various sleep-related diseases including restless leg syndrome (RLS), rapid eye movement sleep behavior disorder (RBD), and obstructive sleep apnea (OSA) [3]. For example, PLMS was found in 80% of RLS patients, 70% of RBD patients, and 19.7% of patients with OSA [4-8].

The third edition of the International Classification of Periodic Sleep Disorders indicates that periodic limb movement disorder (PLMD) should be diagnosed when PLMS occurs more than 15 times/h and is accompanied by sleep disturbance or functional impairment, in the absence of other sleep disorders [9, 10]. The PLMD prevalence in general populations varies from 3.9 to 11% [8, 11, 12]. PLMD may reflect dysregulation of the autonomic system and/or inflammation, and may increase the risks of cardiovascular and cerebrovascular diseases [13]. Medical conditions such as diabetes and migraine have also been associated with PLMD [14].

OSA is caused by upper airway obstruction that triggers recurrent cessation or reduction of airflow during sleep [15]. OSA is diagnosed when the apnea–hypopnea index (AHI) exceeds 5 events/h [15]. Hypoxic effect, arousal intensity, and other metrics can be used to diagnose OSA; however, the AHI correlates better with cardiovascular outcomes [16, 17]. Although OSA and PLMS are known to be associated, the details of their relationship remain unclear [6]; however, a low arousal threshold is common to both OSA and PLMS, and may represent the link between both conditions [18]. PLMS is more frequent in those with mild than no OSA, but far less common in those with severe OSA than in normal participants [19, 20].

OSA can be divided into various subtypes according to the sleeping position. When the AHI in

the supine position is more than double that in the non-supine position, the Cartwright classification identifies positional obstructive sleep apnea (POSA) [21], which accounts for a large proportion of all OSA. Positional treatment of POSA affects the outcomes of continuous positive airway pressure (CPAP) therapy and surgical treatments [22, 23]. POSA may be associated with other sleep disorders. No studies have shown a direct relationship between POSA and PLMS; however, a Danish study investigated sleep positions according to the extent of body (arm, thigh, and upper-back) movements and showed that a preference for the lateral sleep position increased with age and body mass index (BMI), and that the extent of nocturnal body movements was associated with sex, age, BMI, and smoking status [24]. Because age, sex, and BMI are well-known risk factors for OSA, the sleep positions of patients with OSA may be related to nocturnal body movement. Moreover, as body weight unloading or positional changes affect the spinal root muscle response threshold, relationships between either PLMS or low spinal flexor reflex thresholds and enhanced spinal cord excitability have been observed in association to positional changes [25, 26].

However, although several studies have reported relationships between OSA and PLMS [3, 6, 20], there were no studies comparing the prevalence/risk of PLMS with the normal group depending on OSA severity and POSA status. Therefore, our main objectives were to compare PLMS status according to OSA severity and to evaluate the relationship between PLMS and POSA.

Materials and Methods

Data collection

This retrospective study used data from 6,140 patients who complained of sleep apnea or snoring and were recruited at four clinical centers (Seoul National University Hospital, Hallym University Hospital, Seoul Sleep Center, and Lee & Hong Otorhinolaryngology Clinic) from January 2013 to December 2020. Full-night standard polysomnography (PSG) and demographic data were collected. For the analysis of OSA severity and PLMS prevalence, participants who were younger than 19 years old, older than 86 years old, had a total sleep time of less than 180 minutes, missed demographic and polysomnographic data (sex, age, BMI, AHI, and PLMI) were excluded. In addition, participants not diagnosed with OSA, slept less than 30 minutes in each position, and those without AHI data in each position were excluded for the analysis of correlation between POSA and PLMS (Figure 1). The study protocol was approved by the Institutional Review Committee of Seoul National University Hospital (Seoul, Republic of Korea: approval no. C-2007-179-1143), Seoul National University Bundang Hospital (Seongnam-si, Republic of Korea: approval no. B-2010/640-401), and Hallym University College of Medicine (Chuncheon, Republic of Korea: approval no. 2020-03-022).

PSG data collection

A maximum of 21 data streams including electroencephalography, electrooculography, electrocardiography, nasal flow, breathing effort, pulse oximetry, and electromyography of the right and left tibialis anterior muscles were recorded during PSG. Raw data were interpreted by sleep technicians or sleep specialists and annotated in the PSG reports. All sleep, respiratory, and motor events were scored using the American Academy of Sleep Medicine Manual version 2.4 or 2.6 for the Scoring of Sleep and Associated Events during PSG [27].

PLMS and POSA

Limb movements were identified on the electromyograms of both tibialis anterior muscles. Limb movement was defined as an increase of more than 8 μ V in the resting voltage that was sustained for 0.5–10 s [28, 29]. A PLMS series was defined as four consecutive limb movements with 5–90 s

between movements. If the interval between two limb movements was < 5 s, these were considered as a single movement. Respiratory event-related limb movements were not considered as periodic limb movements; such movements occurred between 0.5 s before the start of a respiratory event to 0.5 s after the end of the event. A periodic limb movement index (PLMI) of at least 15/h was considered to indicate PLMS [27, 30].

Apnea events were defined by drops in the oronasal thermal sensor exceeding 90% of the preevent baseline levels, and hypopnea events were defined by drops in signal excursion exceeding 30% that persisted for > 10 s [30]. The AHI was calculated by dividing the total number of apnea and hypopnea events by the total sleep time [30].

We used the Cartwright definition of POSA [31]; thus, the condition was present when difference of 50% or more in AHI between supine and non-supine positions.

Statistical analysis

All statistical analyses were performed using SPSS v26.0 for Windows (*IBM Corp., Armonk, NY, USA*). One-way analysis of variance, independent *t*-tests, and chi-squared tests were performed as appropriate to analyze participant distributions and compare means and standard deviations of PLMI, the periodic limb movements with arousal index (PLMAI), and PLMS. Logistic regression was performed to calculate odds ratios (OR) for PLMS according to OSA phenotype and severity. Among parametric tests, Bonferroni post-hoc test was performed considering equal variance and unequal sample size [32]. Significance was determined at p < 0.05.

Results

A total of 7,745 participants who underwent diagnostic PSG were initially evaluated. A final total

of 6,140 participants were included after the exclusion of participants lacking data on age, gender, BMI, or PLMI. A total of 5,078 patients with OSA were included in the POSA/PLMS correlation study after further exclusion (Figure 1). Baseline characteristics of the participants including mean age, sex, and BMI, as well as the mean total sleep time and the mean AHI, are listed in Table 1. The POSA proportion differed significantly in subgroups divided by OSA severity.

Relationship between PLMS and OSA severity

PLMI, PLMAI, and PLMS values are summarized according to OSA severity in Table 2. The mean (\pm standard deviation) PLMI and PLMAI were 4.22 (\pm 12.02) and 0.84 (\pm 3.67) respectively. The prevalence of PLMS was 9.3%. The mean PLMI of the control group and mild, moderate, and severe OSA groups were 4.29 (\pm 11.35), 6.10 (\pm 16.05), 5.26 (\pm 14.27), and 3.21 (\pm 9.38), respectively. The mean PLMI of patients with severe OSA was significantly lower than those of patients with mild and moderate OSA and did not differ from that of the control group (p = 0.146). The mean PLMI of patients with mild OSA was higher than that of the control group (p = 0.010). No significant differences were observed between the control group and those with mild to moderate OSA. Only the mean PLMAI of patients with severe OSA was significantly lower than those of the other OSA groups; there was no difference between the control group and those with mild or moderate OSA. PLMS prevalence decreased significantly as OSA severity increased 13.1% for the mild OSA group (OR 0.952, 95% confidence interval (CI) [0.677; 1.340], p = 0.779), 11.4% for the moderate OSA group (OR 0.600, 95% CI [0.427–0.842], p = 0.003), and 7.4% for the severe OSA group (OR 0.327, 95% CI [0.233–0.459], p < 0.001) (Table 3).

Association between POSA and PLMS

PLMI, PLMAI, and PLMS values according to sleeping position are listed in Table 4. In the POSA group, the mean PLMI and PLMAI, and PLMS prevalence were 4.8 (\pm 12.7), 0.9 (\pm 3.7), and 11% respectively. However, in the non-POSA group, the values were 2.6 (\pm 9.8), 0.5 (\pm 3.3), and 5.3%, which were significantly lower than in the POSA group (all *p* < 0.001). The mean PLMI was significantly lower in the moderate (*p* = 0.012) and severe (*p* < 0.001) non-POSA group than in the POSA group. Conversely, the mean PLMI increased significantly in the group with mild non-POSA (*p* = 0.012). The mean PLMAI was similarly different in the mild or severe non-POSA and POSA groups (*p* < 0.001), but did not differ between moderate non-POSA and POSA group (*p* = 0.151). Thus, PLMS prevalence increased only in the severe POSA group (*p* < 0.001).

For additional descriptive information about PLMS and sleep apnea in this population, PLMS prevalence increased as patients aged, and PLMS prevalence decreased as patients became obese or male (Supplementary Table 1). There was little correlation between total sleep time and PLMS prevalence. The prevalence of POSA decreased among obese individuals or males, and increased with longer total sleep time (Supplementary Table 2).

The severity of OSA and the prevalence of PLMS between PLMS and non-PLMS group

Logistic regression revealed that PLMS was significantly more common in the POSA group than the non-POSA group (OR 1.389; 95% CI [1.049–1.839]) after adjusting sex, age, BMI, and AHI. However, PLMS was significantly more frequent in POSA than patients with non-POSA only when the former exhibited severe OSA (OR 1.554; 95% CI [1.065–2.267]) (Table 5).

For the relationship between PLMS and the severity of OSA, there was significant association between PLMS and OSA (p < 0.001) (Supplementary Table 3). There was also significant association between PLMS and POSA prevalence (p < 0.001) (Supplementary Table 4).

Discussion

We found significant associations between mean PLMI/PLMAI values and OSA severity, and that the risk of PLMS decreased with OSA severity. The mean PLMI and PLMAI decreased as OSA became more severe. The mean PLMS prevalence in the three OSA subgroups decreased as OSA severity increased. The risk of PLMS was significantly higher in the POSA group than in the non-POSA group only among all Patients with OSA and the severe OSA group, but not in the mild or moderate OSA group.

The reported prevalence of PLMS varied by age, ethnicity, and comorbid disease status. In a Wisconsin, USA sleep cohort, the PLMS rate was 25.3% in a general population [33]. In two German and one Swiss cohorts, the PLMS prevalence rates were 32.4%, 36.4%, and 28.6% respectively [28, 29]; most participants were middle-aged Caucasians. In other studies of Caucasians, the PLMS prevalence reached 61% in older participants but only 5.6% in children [34, 35]. In one community-based study, the PLMS prevalence among African-Americans was 4.3%, in contrast to 9.3% in Caucasians [36]. In South Korea, the PLMS prevalence was 29.3% in older people (mean age, 68.3 ± 5.6 years) [37] and 9.3% in a general population. Thus, age and ethnicity may affect the prevalence of PLMS. PLMS rates in Patients with OSA varied among published studies, at 14.8% and 14.1% in studies conducted in the USA and Korea, respectively [6, 20]. In this study, the PLMS rate for patients with OSA was 9.4%, which is lower than those reported in previous studies, perhaps due to the nature of our participants. PLMS decreases as OSA severity increases. We also reported that the prevalence of PLMS in subgroups with increasing OSA severity were 13.1%, 11.4%, and 7.4% respectively, which were somewhat lower than those of a previous Korean study (17%, 15%, and 12% respectively) [20]. Again, these differences may indicate variation in participant characteristics between studies.

Among all of our patients with OSA, 70.2% exhibited POSA, which is similar to the 75% reported for the HypnoLaus Sleep Cohort [29]. Although the relationship between POSA and PLMS remains poorly understood, three postulates may be advanced. First, a low arousal threshold may be common to both OSA and PLMS, as it is a known risk factor for both conditions [18]. Weijun et al. reported that patients with POSA had a lower arousal threshold than patients with non-POSA [38]. As the proportion of patients with POSA decreases as OSA severity advances, this hypothesis may explain the decreased PLMS prevalence observed in those with severe OSA.

Second, enhanced spinal root reflex responses may trigger PLMS. One USA study found that PLMS was more common in RLS patients with reduced spinal flexor reflexes and enhanced spinal cord excitability [25]. Another study suggested that spinal and supraspinal mechanisms were more important in terms of PLMS than the distal motor efferent and sensory afferent pathways [39]; thus, PLMS may be triggered by frequent spinal cord activations attributable to lowered thresholds, which are affected by body weight unloading and positional changes [26]. Compared to the supine position, standing improved the threshold and reduced the posterior root muscle response, which is a monosynaptic reflex caused by single-pulse, transcutaneous, spinal cord stimulation [26]. In a previous study, the response to a second stimulus decreased and response thresholds were enhanced in the prone position compared to the supine position [40]. Therefore, a more supine sleep position in patients with POSA could decrease the threshold, enhance the response to spinal cord stimulation, and ultimately trigger more PLMS.

Finally, activation of the central pattern generator (CPG) may also explain PLMS. Patients with POSA spend more time than others in supine sleep, [41] which can trigger involuntary lower extremity movements via activation of the CPG [42, 43]. As PLMS may be activated by the CPG, [44] more supine sleep may be associated with more involuntary lower extremity movements attributable to CPG activation. Therefore, POSA may increase PLMS via a positional/CPG

mechanism.

CPAP is a gold standard treatment for OSA [45, 46]. In one meta-analysis, the AHI and systolic blood pressure decreased by up to 33.8 events/h and 2.4 mmHg respectively during CPAP [47]. Such treatment may reduce both airway obstruction and PLMS; accordingly, several hypotheses have been advanced. In a retrospective work exploring the effect of OSA treatment on PLMI, PLMI was found to decrease after CPAP titration in patients with mild OSA, but increased in those with moderate to severe OSA [6][48, 49]. PLMI has been suggested to be classified into induced vs. spontaneous PLMI [8, 48], where induced PLMI is attributable to residual respiratory events and may be treated via CPAP, and spontaneous PLMI is not associated with additional stimulus and remains unmasked after CPAP titration [48, 50]. A similar trend was observed in both an earlier retrospective Korean study and the present work [51]. However, in the Apnea Positive Pressure Long-term Efficacy Study, CPAP titration did not ameliorate PLMI to a greater extent than sham CPAP [6]; the authors performed a second CPAP titration at 6 months after the initial titration, whereas other retrospective studies compared only diagnostic PSG data and CPAP titration status. Given their conflicting results, future research should include long-term follow-up of patients with OSA to meticulously evaluate the efficacy of CPAP treatment.

Our study had several limitations. First, the work was retrospective in nature; we cannot comment on any possible causal relationship between PLMS and OSA. An event-synchronized analysis of a large group that simultaneously considers all respiratory events and limb movements during sleep, as well as sleep stages and positions, is needed. Second, PSG was performed only once. Although single-night studies are reliably diagnostic, individual internight discrepancies may be overlooked [52]. Third, only demographic factors including age, sex and BMI were adjusted when evaluating the effect of OSA on PLMS. Antidepressant use, physical inactivity, and current smoking are all associated with PLMS; however, we did not adjust for these factors [28]. Fourth, the group numbers differed. The number of patients with severe OSA was 3-folds higher than in other groups. As severe patients with OSA exhibit reduced PLMI incidence, such numerical bias may have compromised our interpretation of PLMS prevalence in general populations. Further propensity score matching studies with adjusting for OSA severity may be necessary to reduce significant errors in reaching conclusions. Finally, given the definitions of PLM-related parameters, respiratory events should be clearly identified via event-synchronized analysis. We retrospectively analyzed respiratory event-related limb movements, which must be excluded from PLMS counts; therefore, we used auto-scoring for this variable. Although validated software was employed, the unclear PLMS validation criteria may have led to some bias. Considering possible risk of PLMS in rapid eye movement sleep, further studies related to PLMS during rapid eye movement sleep duration is also needed.

Conclusion

POSA may increase PLMS frequency, especially in patients with severe OSA. If PLMS is suspected, it is important to explore POSA status and assess OSA severity. These actions may improve the selection of an appropriate CPAP treatment.

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ORCiD:

Jae Hyun Soh: 0009-0000-9245-0815 Yun Jin Kang: 0000-0002-7677-4219 Won-Hyuck Yoon: 0000-0001-7942-4196 Chan-Soon Park: 0000-0003-3692-3344 Hyun-Woo Shin: 0000-0002-4038-9992

Author contributions:

Conceptualization, H.-W.S.; methodology, J.H.S., W.-H.Y., H.-W. S.; software, J.H.S., W.-H.Y.; validation, Y.J.K.; formal analysis, Y.J.K., W.-H.Y.; resources, H.-W.S.; data curation, J.H.S., W.-H.Y.; writing—original draft preparation and writing—review and editing, J.H.S., Y.J.K., C.-S.P., H.-W.S.; supervision, C.-S.P., H.-W.S.; project administration, C.-S.P., H.-W.S.; and funding acquisition, H.-W.S., Y.J.K. All authors have read and agreed to the published version of the manuscript.

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References

- Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012 Aug 1;35(8):1039-62.
- Ferri R, Rundo F, Zucconi M, Manconi M, Bruni O, Ferini-Strambi L, et al. An Evidencebased Analysis of the Association between Periodic Leg Movements during Sleep and Arousals in Restless Legs Syndrome. Sleep. 2015 Jun 1;38(6):919-24.
- Gingras JL, Gaultney JF, Picchietti DL. Pediatric periodic limb movement disorder: sleep symptom and polysomnographic correlates compared to obstructive sleep apnea. J Clin Sleep Med. 2011 Dec 15;7(6):603-9a.
- 4. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord. 1997 Jan;12(1):61-5.
- Fantini ML, Michaud M, Gosselin N, Lavigne G, Montplaisir J. Periodic leg movements in REM sleep behavior disorder and related autonomic and EEG activation. Neurology. 2002 Dec 24;59(12):1889-94.
- Budhiraja R, Javaheri S, Pavlova MK, Epstein LJ, Omobomi O, Quan SF. Prevalence and correlates of periodic limb movements in OSA and the effect of CPAP therapy. Neurology. 2020 Apr 28;94(17):e1820-e7.
- Rye DB, Trotti LM. Restless legs syndrome and periodic leg movements of sleep. Neurol Clin.
 2012 Nov;30(4):1137-66.
- 8. Drakatos P, Olaithe M, Verma D, Ilic K, Cash D, Fatima Y, et al. Periodic limb movements during sleep: a narrative review. Journal of Thoracic Disease. 2021;13(11):6476-94.

- 9. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014 Nov;146(5):1387-94.
- Joseph V, Nagalli S. Periodic Limb Movement Disorder. StatPearls. Treasure Island (FL): StatPearls PublishingCopyright © 2023, StatPearls Publishing LLC.; 2023.
- Hornyak M, Feige B, Riemann D, Voderholzer U. Periodic leg movements in sleep and periodic limb movement disorder: prevalence, clinical significance and treatment. Sleep Med Rev. 2006 Jun;10(3):169-77.
- 12. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res. 2002 Jul;53(1):547-54.
- Figorilli M, Puligheddu M, Congiu P, Ferri R. The Clinical Importance of Periodic Leg Movements in Sleep. Curr Treat Options Neurol. 2017 Mar;19(3):10.
- Tiseo C, Vacca A, Felbush A, Filimonova T, Gai A, Glazyrina T, et al. Migraine and sleep disorders: a systematic review. J Headache Pain. 2020 Oct 27;21(1):126.
- Laratta CR, Ayas NT, Povitz M, Pendharkar SR. Diagnosis and treatment of obstructive sleep apnea in adults. Cmaj. 2017 Dec 4;189(48):E1481-e8.
- 16. Huang W, Zhang X, Wang X, Zhou T, Zhao X, Xu H, et al. Effects of obstructive sleep apnea during rapid eye movement sleep on cardiac autonomic dysfunction: Results from the Shanghai sleep health study cohort. J Sleep Res. 2023 Oct;32(5):e13904.
- 17. Malhotra A, Ayappa I, Ayas N, Collop N, Kirsch D, McArdle N, et al. Metrics of sleep apnea severity: beyond the apnea-hypopnea index. Sleep. 2021 Jul 9;44(7).
- Wang Q, Li Y, Li J, Wang J, Shen J, Wu H, et al. Low Arousal Threshold: A Potential Bridge Between OSA and Periodic Limb Movements of Sleep. Nat Sci Sleep. 2021;13:229-38.
- Warnes H, Dinner DS, Kotagal P, Burgess RC. Periodic limb movements and sleep apnoea. J Sleep Res. 1993 Mar;2(1):38-44.
- 20. Lee SA, Kim SJ, Lee SY, Kim HJ. Periodic limb movements during sleep are associated with

poor health-related quality of life in patients with obstructive sleep apnea. Sleep Breath. 2022 Sep;26(3):1045-52.

- 21. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS. Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. Sleep Med Rev. 2014 Feb;18(1):7-17.
- 22. Sabil A, Blanchard M, Trzepizur W, Goupil F, Meslier N, Paris A, et al. Positional obstructive sleep apnea within a large multicenter French cohort: prevalence, characteristics, and treatment outcomes. Journal of Clinical Sleep Medicine. 2020;16(12):2037-46.
- 23. Lee CH, Shin HW, Han DH, Mo JH, Yoon IY, Chung S, et al. The implication of sleep position in the evaluation of surgical outcomes in obstructive sleep apnea. Otolaryngol Head Neck Surg. 2009 Apr;140(4):531-5.
- 24. Skarpsno ES, Mork PJ, Nilsen TIL, Holtermann A. Sleep positions and nocturnal body movements based on free-living accelerometer recordings: association with demographics, lifestyle, and insomnia symptoms. Nat Sci Sleep. 2017;9:267-75.
- Bara-Jimenez W, Aksu M, Graham B, Sato S, Hallett M. Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. Neurology. 2000 Apr 25;54(8):1609-16.
- Megía-García Á, Serrano-Muñoz D, Comino-Suárez N, Del-Ama AJ, Moreno JC, Gil-Agudo A, et al. Effect of posture and body weight loading on spinal posterior root reflex responses. Eur J Neurosci. 2021 Oct;54(7):6575-86.
- 27. Berry RB, Gamaldo CE, Harding SM, Brooks R, Lloyd RM, Vaughn BV, et al. AASM Scoring Manual Version 2.2 Updates: New Chapters for Scoring Infant Sleep Staging and Home Sleep Apnea Testing. J Clin Sleep Med. 2015 Nov 15;11(11):1253-4.
- 28. Szentkirályi A, Stefani A, Hackner H, Czira M, Teismann IK, Völzke H, et al. Prevalence and associated risk factors of periodic limb movement in sleep in two German population-based studies. Sleep. 2019 Mar 1;42(3).

- 29. Haba-Rubio J, Marti-Soler H, Marques-Vidal P, Tobback N, Andries D, Preisig M, et al. Prevalence and determinants of periodic limb movements in the general population. Ann Neurol. 2016 Mar;79(3):464-74.
- Richard B. Berry RB, Charlene E. Gamaldo, Susan M. Harding, Robin M. Lloyd, Carole L. Marcus, Bradley V. Vaughn. The AASM manual for the scoring of sleep and associated events. Rules, Terminology and Technical Specifications. American Academy of Sleep Medicine. 2012.
- Oulhaj A, Al Dhaheri S, Su BB, Al-Houqani M. Discriminating between positional and nonpositional obstructive sleep apnea using some clinical characteristics. Sleep Breath. 2017 Dec;21(4):877-84.
- 32. Shingala MC. Comparison of Post Hoc Tests for Unequal Variance. 2015.
- 33. Leary EB, Moore HEt, Schneider LD, Finn LA, Peppard PE, Mignot E. Periodic limb movements in sleep: Prevalence and associated sleepiness in the Wisconsin Sleep Cohort. Clin Neurophysiol. 2018 Nov;129(11):2306-14.
- 34. Claman DM, Ewing SK, Redline S, Ancoli-Israel S, Cauley JA, Stone KL. Periodic leg movements are associated with reduced sleep quality in older men: the MrOS Sleep Study. J Clin Sleep Med. 2013 Nov 15;9(11):1109-17.
- 35. Marcus CL, Traylor J, Gallagher PR, Brooks LJ, Huang J, Koren D, et al. Prevalence of periodic limb movements during sleep in normal children. Sleep. 2014 Aug 1;37(8):1349-52.
- Scofield H, Roth T, Drake C. Periodic limb movements during sleep: population prevalence, clinical correlates, and racial differences. Sleep. 2008 Sep;31(9):1221-7.
- 37. Kang S, Yoon I. The prevalence and impact on sleep of periodic limb movements during sleep in the elderly. Sleep Medicine. 2013 2013/12/01/;14:e165-e6.
- 38. Huang W, Wang X, Xu C, Xu H, Zhu H, Liu S, et al. Prevalence, characteristics, and respiratory arousal threshold of positional obstructive sleep apnea in China: a large scale study

from Shanghai Sleep Health Study cohort. Respir Res. 2022 Sep 12;23(1):240.

- 39. Chada A, Hoque R. Images: Periodic Limb Movements During Sleep Noted on Ventral Thigh Surface Electromyography in an Above-the-Knee Amputated Stump. J Clin Sleep Med. 2019 Aug 15;15(8):1183-4.
- 40. Danner SM, Krenn M, Hofstoetter US, Toth A, Mayr W, Minassian K. Body Position Influences Which Neural Structures Are Recruited by Lumbar Transcutaneous Spinal Cord Stimulation. PLoS One. 2016;11(1):e0147479.
- 41. Sabil A, Blanchard M, Trzepizur W, Goupil F, Meslier N, Paris A, et al. Positional obstructive sleep apnea within a large multicenter French cohort: prevalence, characteristics, and treatment outcomes. J Clin Sleep Med. 2020 Dec 15;16(12):2037-46.
- 42. Klarner T, Zehr EP. Sherlock Holmes and the curious case of the human locomotor central pattern generator. J Neurophysiol. 2018 Jul 1;120(1):53-77.
- 43. Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G, Green BA. Involuntary stepping after chronic spinal cord injury. Evidence for a central rhythm generator for locomotion in man. Brain. 1994 Oct;117 (Pt 5):1143-59.
- 44. Guertin PA. Central pattern generator for locomotion: anatomical, physiological, and pathophysiological considerations. Front Neurol. 2012;3:183.
- 45. Kakkar RK, Berry RB. Positive airway pressure treatment for obstructive sleep apnea. Chest. 2007 Sep;132(3):1057-72.
- Stuck BA, Leitzbach S, Maurer JT. Effects of continuous positive airway pressure on apneahypopnea index in obstructive sleep apnea based on long-term compliance. Sleep Breath. 2012 Jun;16(2):467-71.
- 47. Jonas DE, Amick HR, Feltner C, Weber RP, Arvanitis M, Stine A, et al. Screening for Obstructive Sleep Apnea in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2017 Jan 24;317(4):415-33.

- 48. Baran AS, Richert AC, Douglass AB, May W, Ansarin K. Change in periodic limb movement index during treatment of obstructive sleep apnea with continuous positive airway pressure. Sleep. 2003 Sep;26(6):717-20.
- 49. Lin T-C, Zeng B-Y, Wu M-N, Chen T-Y, Chen Y-W, Yeh P-Y, et al. Changes in Periodic Limb Movements of Sleep After the Use of Continuous Positive Airway Pressure Therapy: A Meta-Analysis. Frontiers in Neurology. 2022 2022-June-02;13.
- 50. Hedli LC, Christos P, Krieger AC. Unmasking of periodic limb movements with the resolution of obstructive sleep apnea during continuous positive airway pressure application. J Clin Neurophysiol. 2012 Aug;29(4):339-44.
- 51. Lee SA, Kim SJ, Lee SY, Kim HJ. Clinical characteristics of periodic limb movements during sleep categorized by continuous positive airway pressure titration polysomnography in patients with obstructive sleep apnea. Sleep Breath. 2022 Mar;26(1):251-7.
- 52. Sforza E, Haba-Rubio J. Night-to-night variability in periodic leg movements in patients with restless legs syndrome. Sleep Med. 2005 May;6(3):259-67.

Table 1. Baseline characteristics of patients.

Characteristics	Total	Control (AHI < 5)	$Mild OSA$ $(5 \le AHI < 15)$	$Moderate OSA$ $(15 \le AHI < 30)$	Severe OSA (30 ≤ AHI)	p value
Number of cases	6,140	784	941	1,280	3,135	< 0.001
Age (yr) †	45.09 ± 14.21	35.65 ± 13.37	42.51 ± 14.26	46.45 ± 13.97	47.66 ± 13.37	< 0.001
BMI (kg/m^2) †	25.56 ± 4.04	22.57 ± 3.11	24.06 ± 3.43	25.03 ± 3.41	26.97 ± 4.04	< 0.001
Male (%) ‡	78.5	49.7	68.2	78.1	88.9	< 0.001
TST (min) †	302.53 ± 62.84	322.72 ± 61.11	319.40 ± 60.63	313.22 ± 62.23	288.05 ± 60.63	< 0.001
AHI (events/hr) †	35.57 ± 27.03	1.96 ± 1.46	9.76 ± 2.97	22.20 ± 4.31	57.18 ± 19.93	< 0.001
Ratio of POSA (%) ‡	70.2		85.9	84.3	59.8	< 0.001

OSA: Obstructive sleep apnea, AHI: Apnea hypopnea index, BMI: Body mass index, TST: Total sleep time, POSA: Positional obstructive sleep apnea

[†] ANOVA test, [‡] Chi square test were used

Table 2. Relationship between periodic limb movement during sleep and the severity of obstructive sleep apnea.

Parameters	Total	Control		OSA		<i>p</i> value
	(n = 6, 140)	(n = 784)	Mild	Moderate	Severe	-
			(n = 941)	(n = 1,280)	(n = 3,135)	
PLMI (events/hr)	4.22 ± 12.02	4.29 ± 11.35	6.10 ± 16.05	5.26 ± 14.27	3.21 ± 9.38	< 0.001†
PLMAI (events/hr)	0.84 ± 3.67	1.38 ± 4.69	1.26 ± 3.92	1.06 ± 4.46	0.50 ± 2.82	< 0.001†
PLMS (%)	9.3	8.7	13.1	11.4	7.4	< 0.001‡

OSA: Obstructive sleep apnea, PLMI: Periodic limb movements index, PLMAI: Periodic limb movements with arousal index, PLMS: Periodic limb

movements during sleep

Data were expressed as mean \pm standard deviation

† p value of ANOVA test and *‡* Chi square test mong mild, moderate, and severe OSA group were used.

Table 3. Risk of p	eriodic limb movemen	ts during sleep acc	ording to the seve	erity of obstructive sleep apnea.	
I word of I thon of p	er roure mins movemen	is during sleep dee	or anna co ene ser	city of obscitactive sieep apricat	

OSA severity	Total	PLMS (%)	OR (95% CI)*	<i>p</i> value
Control	784	68 (8.7)		
Mild	941	123 (13.1)	0.952 (0.677 - 1.340)	0.779
Moderate	1,280	146 (11.4)	0.600 (0.427 - 0.842)	0.003
Severe	3,135	233 (7.4)	0.327 (0.233 - 0.459)	< 0.001
		× /		

OSA: Obstructive sleep apnea, PLMS: Periodic limb movements during sleep, OR: Odds ratio, CI: Confidence index

* Odds ratio were adjusted for the sex, age and BMI.

Doromotoro		Total			Mild OSA ≤ AHI < 15)			oderate OSA ≤ AHI < 30)			Severe OSA (30 ≤ AHI)	
Parameters	POSA (n=3,565)	Non-POSA (n=1,513)	p value	POSA (n=759)	Non-POSA (n=124)	p value	POSA (n=1,018)	Non-POSA (n=191)	p value	POSA (n=1,788)	Non-POSA (n=1,198)	p value
PLMI (events/hour)	4.8 ± 12.7	2.6 ± 9.8	<0.001†	5.4 ± 14.4	7.8 ± 20.7	0.012†	5.6 ± 14.8	3.6 ± 12.9	0.012†	4.1 ± 10.5	1.9 ± 6.9	<0.001†
PLMAI (events/hour)	0.9 ± 3.7	0.5 ± 3.3	< 0.001†	1.1 ± 3.6	2.2 ± 6.1	<0.001†	1.1 ± 4.0	1.2 ± 6.9	0.151†	0.7 ± 3.5	0.2 ± 1.4	<0.001†
PLMS (%)	11.0	5.3	<0.001‡	12.1	14.5	0.454‡	12.2	7.9	0.085‡	9.8	3.9	<0.001‡

Table 4. Effects of positional obstructive sleep apnea on periodic limb movements during sleep.

PLMI: Periodic limb movements index, PLMAI: Periodic limb movements with arousal index, PLMS: Periodic limb movements during sleep, POSA:

Positional obstructive sleep apnea

[†] Independent sample T test, [‡] Chi square test

Table 5. Risk of periodic limb movements during sleep according to positional obstructive sleep apnea status.

	POSA		on-POSA	OR (95% CI)*	<i>p</i> value	
Total	PLMS (%)	Total	PLMS (%)			
3,565	392 (11.0)	1,513	80 (5.3)	1.389 (1.049 – 1.839)	0.022	
759	92 (12.1)	124	18 (14.5)	0.559 (0.303 - 1.030)	0.062	
1,018	124 (12.2)	191	15 (7.9)	1.822 (0.995 - 3.339)	0.052	
1,788	176 (9.8)	1,198	47 (3.9)	1.554 (1.065 – 2.267)	0.022	
	3,565 759 1,018	Total PLMS (%) 3,565 392 (11.0) 759 92 (12.1) 1,018 124 (12.2)	Total PLMS (%) Total 3,565 392 (11.0) 1,513 759 92 (12.1) 124 1,018 124 (12.2) 191	Total PLMS (%) Total PLMS (%) 3,565 392 (11.0) 1,513 80 (5.3) 759 92 (12.1) 124 18 (14.5) 1,018 124 (12.2) 191 15 (7.9)	Total PLMS (%) Total PLMS (%) 3,565 392 (11.0) 1,513 80 (5.3) 1.389 (1.049 – 1.839) 759 92 (12.1) 124 18 (14.5) 0.559 (0.303 - 1.030) 1,018 124 (12.2) 191 15 (7.9) 1.822 (0.995 - 3.339)	

OSA: Obstructive sleep apnea, POSA: Positional obstructive sleep apnea, PLMS: Periodic limb movements during sleep, OR: Odds ratio, CI: Confidence

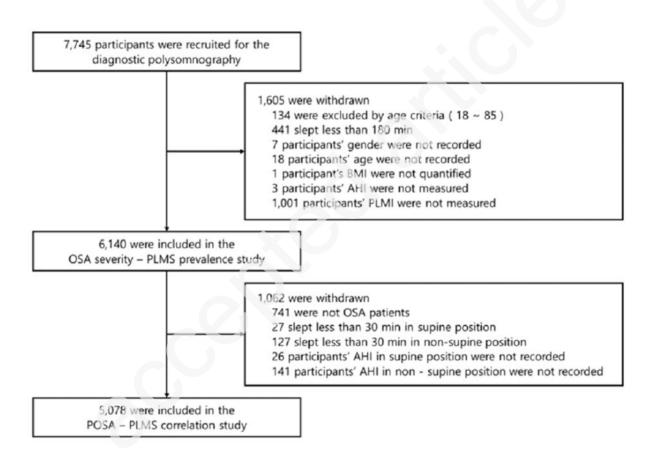
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* Odds ratio were adjusted for the sex, age, body mass index and apnea-hypopnea index.

Figure Legends

Figure 1. The study flowchart.

BMI: Body mass index, AHI: Apnea hypopnea index, PLMI: Periodic limb movements index, OSA: Obstructive sleep apnea, PLMS: Periodic limb movements during sleep, POSA: Positional obstructive sleep apnea



Supplementary Table 1. Risk of periodic limb movements during sleep according to each parameter.

Parameters	OR (95% CI) †	<i>p</i> value
Age	1.069 (1.061 - 1.076)	< 0.001
BMI	0.961 (0.936 - 0.986)	0.003
TST	1.000 (0.999 – 1.002)	0.726
Male		< 0.001‡

OR: Odds ratio, CI: Confidence index, BMI: Body mass index, TST: Total sleep time

[†] Odds ratio were adjusted for the other parameters including the severity of obstructive sleep apnea.

[‡] Chi square test was used.

Supplementary Table 2. Risk of positional obstructive sleep apnea during sleep according to each parameter.

Parameters	OR (95% CI) †	<i>p</i> value
Age	1.000 (0.996 - 1.005)	0.849
BMI	0.835 (0.821 - 0.850)	< 0.001
TST	1.007 (1.006 – 1.008)	< 0.001
Male		0.029‡

OR: Odds ratio, CI: Confidence index, BMI: Body mass index, TST: Total sleep time

[†] Odds ratio were adjusted for the other parameters including the severity of obstructive sleep apnea.

[‡] Chi square test was used.

Supplementary Table 3. Relationship between periodic limb movement during sleep and the severity of obstructive sleep apnea.

	Total	Mild OSA	Moderate OSA	Severe OSA	<i>p</i> value
PLMS	473	111 (23.5%)	138 (29.2%)	224 (47.3%)	< 0.001
Non-PLMS	4,602	763 (16.6%)	1,068 (23.2%)	2,771 (60.2%)	< 0.001

OSA: Obstructive sleep apnea, PLMS: Periodic limb movements during sleep

Chi square test was used.

Supplementary Table 4. Relationship between periodic limb movement during sleep and the

prevalence of positional obstructive sleep apnea.

Total	POSA	Non-POSA	<i>p</i> value
473	392 (82.9%)	81 (17.1%)	< 0.001
4,602	3,165 (68.8%)	1,437 (31.2%)	<0.001
	473	473 392 (82.9%)	473 392 (82.9%) 81 (17.1%)

POSA: Positional obstructive sleep apnea, PLMS: Periodic limb movements during sleep

Chi square test was used.