JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2022;18(3):351-357 / https://doi.org/10.3988/jcn.2022.18.3.351

Sex Differences in Excessive Daytime Sleepiness Among Patients With Obstructive Sleep Apnea

Sang-Ahm Lee
Kayeong Im
Ha-rin Yang
Hyo Jae Kim

Department of Neurology,
Asan Medical Center,
University of Ulsan College of Medicine,
Seoul, Korea

Background and Purpose To identify sex differences in daytime sleepiness associated with apnea severity and periodic limb movements during sleep (PLMS) in subjects with obstructive sleep apnea (OSA).

Methods This study used the Epworth Sleepiness Scale (ESS), Beck Depression Inventory (BDI), and Sleep Hygiene Index (SHI) in logistic regression analyses with interaction terms. Severe OSA, excessive daytime sleepiness (EDS), and PLMS were defined as an apnea-hypopnea index of ≥30, an ESS score of ≥11, and a periodic limb movements index of >15, respectively.

Results The 1,624 subjects with OSA (males, 79.1%) comprised 45.3%, 38.2%, and 16.4% with severe OSA, EDS, and PLMS, respectively. Multiple logistic regression without interaction terms showed that sex, severe OSA, and PLMS were not significantly associated with EDS. However, significant interactions were noted between sex and severe OSA and PLMS in EDS in both crude and adjusted models (all p values<0.05). In the adjusted model, severe OSA was associated with EDS in males (p=0.009) but not in females. PLMS were more likely to be associated with EDS in females (p=0.013), whereas PLMS were less likely to be associated with EDS in males (p=0.041). The models were adjusted by the BDI score, SHI, and presence of medical comorbidities.

Conclusions There are significant sex differences in subjective daytime sleepiness in subjects with severe OSA and PLMS. Severe OSA and PLMS may influence daytime sleepiness more in males and females, respectively.

Keywords obstructive sleep apnea; excessive daytime sleepiness; periodic limb movements during sleep; sex differences.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common type of sleep-disordered breathing, in which collapse of the upper airway results in recurrent and transient cessation or reduction of the airflow during sleep.[1] OSA is a significant risk factor for all-cause mortality.[2] A common and important characteristic of the clinical presentation of OSA is excessive daytime sleepiness (EDS).[1] EDS may contribute to mood disturbance and neurocognitive impairments in individuals with OSA[3,4] and, furthermore, is potentially dangerous because of the increased risk of traffic collisions and occupational accidents.[5] In general, OSA is more common and severe in males than in females,[1] but it is inconclusive whether sex differences in EDS exist in individuals with OSA:[6] some studies have found no sex differences,[6,7] while others have found either females or males have a higher prevalence of OSA.[6,8]

The mechanisms underlying EDS in patients with OSA are complicated and multifactorial.[9] Although various factors such as age, sex, obesity, depression, and other medical illnesses may play an important role,[9] disturbance of the sleep architecture–including inter-

Received September 14, 2021
Revised November 25, 2021
Accepted November 25, 2021

Correspondence
Sang-Ahm Lee, MD
Department of Neurology,
Asan Medical Center,
University of Ulsan College of Medicine,
88 Olympic-ro 43-gil, Songpa-gu,
Seoul 05505, Korea
Tel +82-2-3010-3445
Fax +82-2-474-4691
E-mail salee@amc.seoul.kr

mittent hypoxemia and frequent arousal resulting from sleep apneas–has been considered one of the most important predictors for EDS.[10] Patients with severe OSA have a worse sleep architecture including more N1 sleep and less N3 and rapid eye movement (REM) sleep.[11] Therefore, there may be a direct relationship between EDS and the severity of OSA, although some studies have not found a strong linear relationship of EDS with the apnea-hypopnea index (AHI) in OSA patients.[10,12] Nevertheless, continuous positive airway pressure (CPAP) treatment is effective for controlling daytime sleepiness in individuals with severe OSA.[13] Whether the effects of apnea severity on daytime sleepiness differ between males and females remains to be confirmed, but there is evidence supporting a sex difference.[14] Specifically, daytime sleepiness was found to not be correlated with AHI at mild-to-moderate levels in females, and have a weaker association in females than in males with severe OSA.[14]

Periodic limb movements during sleep (PLMS) are involuntary leg movements that occur repetitively during sleep.[15] PLMS are common, with a reported prevalence of 29%–36% among adults in the general population.[16,17] Given that PLMS are often accompanied by arousal, thereby disrupting nocturnal sleep,[18] these movements may be another important causative factor for EDS. For example, sleepy individuals with OSA despite treatment with CPAP are likely to have PLMS.[19] However, most studies have found that PLMS do not result in daytime sleepiness.[16,17] The literature on sex differences in the association between PLMS and daytime sleepiness is inconsistent. Among female OSA patients, those with PLMS had less subjective sleepiness than those without PLMS, but male OSA patients did not show such a difference.[20] In contrast, another previous study found that PLMS were negatively correlated with EDS in males with OSA.[21] Thus, how sex influences the relationships of apnea severity and PLMS with daytime sleepiness has not been clearly identified in OSA patients. Therefore, we examined sex differences in the associations of daytime sleepiness with apnea severity and PLMS in subjects with OSA.

METHODS

Subjects

Subjects with suspected OSA who visited a sleep center between January 2009 and March 2015 were consecutively recruited for this cross-sectional study. The inclusion criteria were being ≥18 years of age and having a new diagnosis of OSA based on polysomnography (PSG). Subjects were excluded if they had a total sleep time of <180 min as measured by PSG, if they had narcolepsy, or if their data were incomplete. Demographic data, medical histories, and use of drugs were collected from the electronic medical charts and self-reported checklists. Written informed consent was obtained from all participants. The study was reviewed and approved by the Institutional Review Board of Asan Medical Center (2021-0390).

Polysomnography

Overnight standard PSG was conducted in a sleep laboratory. Polysomnograms obtained before and after November 2013 were scored based on the 2007 and 2012 manuals of the American Academy of Sleep Medicine, respectively.[22,23] An episode of apnea was scored when the peak thermal sensor excursion reduced by ≥90% of the pre-event baseline for ≥10 seconds. Hypopnea was scored using a nasal pressure sensor when the peak signal excursion reduced by ≥30% of the pre-event baseline for ≥10 seconds, along with a ≥4% reduction in O_2 saturation for PSG recordings made before November 2013,[22] or with either a ≥3% reduction in O_2 saturation or an associated arousal for PSG recordings made after November 2013 in our laboratory.[23] The AHI was quantified as the average number of apnea and hypopnea episodes per hour of sleep. OSA was defined by an AHI of ≥5 events per sleep hour on PSG. The severity of sleep apnea was categorized according to the AHI into mild (5≤AHI<15), moderate (15≤AHI<30), and severe (AHI≥30).

Events of leg movements were collected from the bilateral tibialis anterior using the following parameters: sampling frequency of 200 Hz, 10–90 Hz filtering, and sensitivity of 10 μV/mm. An event of leg movement was defined as an increase of ≥8 μV in the electromyography voltage above the resting value that lasted for 0.5–10 seconds.[22,23] A periodic leg movement series was defined as at least four consecutive leg movement events with a period of 5–90 seconds between the leg movements. Leg movements in bilateral legs with an interval of <5 seconds were considered a single leg movement. Respiratory event-related leg movements were excluded from the scoring of periodic leg movements when the leg movements occurred during the period from 0.5 seconds preceding a respiratory event to 0.5 seconds after the event.[22,23] The presence of PLMS was defined as a periodic leg movements index (PLMI) of >15, corresponding to the number of leg movements collected by definition per hour.

Measures

The Epworth Sleepiness Scale (ESS) is a self-reported eight-item questionnaire asking how often the individual feels sleepy during daytime activities.[24] Each item is scored from 0 to 3, resulting in lowest and highest possible scores of 0 and 24, respectively. A higher score represents greater daytime sleepiness, and EDS was defined as an ESS score of ≥11. The Beck

Depression Inventory (BDI) is a self-reported 21-item questionnaire on how an individual has been feeling during the past week.[25] Each item is scored from 0 to 3, and hence the total score ranges from 0 to 63, with a higher score representing greater depressed mood. Sleep hygiene was assessed using the Sleep Hygiene Index (SHI),[26] which comprises 13 items scored from 1 to 5. The total score therefore ranges from 13 to 65, with a higher score indicating worse sleep hygiene.

Statistical analysis

Student's *t*-test, the Mann–Whitney U test, and the Pearson's chi-square test were used for statistical analysis depending on the type and distribution of the variable. To determine sex interactions with OSA, PLMS, and EDS, a logistic regression analyses with interaction terms were performed using an ESS score of ≥11 as the dependent variable. Sex, an AHI of ≥30, and a PLMI of >15 were used as the independent variables. The models were adjusted by the confounding variables exhibiting a p value <0.05 in univariate analysis. Variables with a condition index of >30 or a variance inflation factor of >10 were excluded due to the assumed presence of multicollinearity. We used the Hosmer–Lemeshow test to evaluate the goodness of fit of a statistical model. Statistical analyses were conducted with the Statistical Package for the Social Sciences (version 21.0, IBM Corp., Armonk, NY, USA). A two-tailed p value <0.05 was considered significant.

RESULTS

Subjects

Of 1,661 consecutive subjects with an AHI of ≥5 enrolled during the study period, 37 subjects were excluded due to a total sleep time of <180 min (n=21), narcolepsy (n=3), or incomplete data (n=13). The remaining 1,624 subjects with OSA were included in the study (Table 1). The medical comorbidities noted included medical disorders (n=168), neurological

Table 1. Subject characteristics and comparisons thereof depending on excessive daytime sleepiness in males and females with obstructive sleep apnea

	Total (n=1,624)	Males (n=1,284)		Females (n=340)	
		ESS score <11 (n=787)	ESS score ≥11 (n=497)	ESS score <11 (n=217)	ESS score ≥11 (n=123)
Age (yr)	51.4±11.7	50.9±11.9	48.8±11.7†	56.0±10.3	56.3±9.5
BMI (kg/m^2)	26.1±3.8	26.1±3.5	26.9±3.8§	24.8±4.0	25.5±3.9
Hypertension	577 (35.5)	286 (36.3)	166 (33.4)	75 (34.6)	50 (40.7)
Diabetes mellitus	188 (11.6)	94 (11.9)	53 (10.7)	21 (9.7)	20 (16.3)
Medical comorbidities	270 (16.6)	121 (15.4)	79 (15.9)	43 (19.8)	27 (22.0)
ESS score	9.4±5.3	6.0±2.8	14.6±3.2§	6.0±2.8	15.8±4.0§
AHI	27.3 [15.1–46.0]	28.0 [16.0–45.3]	32.0 [18.2–52.0]†	20.5 [11.4–35.4]	17.0 [10.0–28.3]
AHI ≥30	735 (45.3)	369 (46.9)	270 (54.3)†	68 (31.3)	28 (22.8)*
PLMI >15	267 (16.4)	137 (17.4)	68 (13.7)*	31 (14.3)	31 (25.2)†
PLMAI >5	77 (4.7)	39 (5.0)	18 (3.6)	11 (5.1)	9 (7.3)
Total arousal index (/h)	34.7±17.1	35.2±15.1	38.0±20.0†	29.0±15.2	28.0±17.3
BDI score	10.2±7.7	8.4±7.0	11.1±7.3§	11.3±8.3	16.2±8.8§
SHI	23.0±9.0	22.2±9.1	25.0±9.19§	20.5±8.1	24.3±8.2§
Subjective sleep quantity (h)	6.4±1.3	6.5±1.3	6.2±1.4†	6.2±1.3	6.1±1.6
Sleep architecture					
N1 (min)	106.9±53.3	111.4±48.2	117.6±59.3†	82.0±41.9	79.1±54.2
N2 (min)	149.1±49.4	147.5±46.5	146.6±52.7	156.5±48.5	156.0±53.2
N3 (min)	17.8 [1.5–46.0]	13.0 [0.5–40.0]	15.0 [0.5–41.3]	35.0 [9.3–59.8]	32.5 [7.5–66.0]
REM (min)	58.4±25.6	55.4±24.3	60.2±26.5†	61.7±24.8	64.2±29.6
TST (min)	342.2±47.4	338.5±46.3	349.5±48.1§	340.4±46.1	339.4±51.3
Sleep latency (min)	3.5 [1.5–7.5]	3.6 [2.0–7.5]	3.0 [1.5–5.5]§	4.5 [2.5–10.5]	3.5 [1.5–8.0]
WASO (min)	26.4 [13.0–51.4]	28.0 [14.0–51.8]	21.5 [11.0–45.0]§	30.5 [15.2–58.5]	30.1 [14.5–60.0]
Sleep efficiency (%)	91.4 [84.3–95.5]	90.6 [84.0–95.0]	93.3 [86.0–96.0]§	90.2 [82.0–95.2]	90.3 [80.8–95.3]

Data are n (%), mean±standard deviation, or median [interquartile range] values.
*p<0.1; †p<0.05; ‡p<0.01; §p<0.001.
AHI, apnea-hypopnea index; BDI, Beck Depression Inventory; BMI, body mass index; ESS, Epworth Sleepiness Scale; PLMAI, periodic limb movements arousal index; PLMI, periodic limb movements index; REM, rapid eye movement; SHI, Sleep Hygiene Index; TST, total sleep time; WASO, wake after sleep onset.

diseases (*n*=72), and psychiatric disorders (*n*=30). Overall, medical comorbidities were more common in females (20.6%) than in males (15.6%) (*p*=0.027). Severe OSA was more common in males (49.8%) than in females (28.2%) (*p*<0.001), while 24.4% (*n*=397) of all subjects had mild OSA and 30.3% (*n*=492) had moderate OSA. The proportions of subjects with PLMS and EDS did not differ between females and males overall.

The proportions of subjects with EDS did not differ depending on presence of severe OSA or PLMS in males and females (Table 1). Severe OSA was particularly prevalent among males with an ESS score of ≥11. However, PLMS were less common in males with an ESS score of ≥11 than in those with an ESS score of <11, but more common in females with an ESS score of ≥11 than in those with an ESS score of <11. For both male and female subjects, the BDI score and SHI were positively associated with an ESS score of ≥11 (all *p* values<0.001). With regard to sleep architecture, males spent more time in N1 sleep and less time in N2, N3, and REM sleep; had a shorter sleep latency and wake-after-sleep-onset time; and had a higher sleep efficiency than females.

Table 2. Results of logistic regression analysis revealing factors associated with EDS in patients with OSA (*n*=1,624)

Model and variables	ESS score ≥11		
	OR	95% CI	*p*
Model without interaction*			
Sex, male	1.225	0.938–1.600	0.136
AHI ≥30	1.208	0.979–1.490	0.078
PLMI >15	0.910	0.687–1.206	0.512
Model with interaction of sex and severe OSA†			
Males with AHI <30	1.000		
Males with AHI ≥30	1.366	1.084–1.722	0.008
Females with AHI <30	1.027	0.747–1.412	0.870
Females with AHI ≥30	0.673	0.413–1.095	0.111
Model with interaction of sex and PLMS‡			
Males with PLMI ≤15	1.000		
Males with PLMI >15	0.708	0.510–0.982	0.038
Females with PLMI ≤15	0.669	0.497–0.901	0.008
Females with PLMI >15	1.378	0.805–2.359	0.242

*Adjusted by BDI score, SHI, and the presence of medical comorbidities; †Adjusted by PLMI >15, BDI score, SHI, and the presence of medical comorbidities; ‡Adjusted by AHI ≥30, BDI score, SHI, and the presence of medical comorbidities.
AHI, apnea-hypopnea index; BDI, Beck Depression Inventory; CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OR, odds ratio; OSA, obstructive sleep apnea; PLMS, periodic limb movements during sleep; PLMI, periodic limb movements index; SHI, Sleep Hygiene Index.

Sex interaction with OSA and PLMS on EDS

A multiple logistic regression without interaction terms showed that all independent variables (sex, AHI ≥30, and PLMI >15) were not significantly associated with an ESS score of ≥11, although an AHI of ≥30 almost reached statistical significance (*p*=0.078) (Table 2). The model was adjusted by BDI score, SHI, and presence of medical comorbidity. Body mass index, total arousal index, total sleep time, and subjective sleep quantity at home were excluded from the model due to a condition index of >30, and age was removed from the model because *p* was <0.05 in a Hosmer–Lemeshow test.

Compared with males with an AHI of <30, the odds ratio (OR) for an ESS score of ≥11 was higher in males with an AHI of ≥30, but not in females regardless of the AHI (Table 2). In contrast, compared with males with a PLMI of ≤15, the OR for an ESS score of ≥11 was lower in males with a PLMI of >15 and females with a PLMI of ≤15, but not in females with a PLMI of >15.

The effects of sex interaction with severe OSA and PLMS on EDS were significant in both the crude and adjusted models (all *p* values<0.05) (Table 3). Specifically, in the adjusted model, an AHI of ≥30 was associated with an ESS score of ≥11 in males (OR=1.359, 95% confidence interval [CI]= 1.079–1.713, *p*=0.009), but not in females (*p*=0.113). A PLMI of >15 was more likely to be associated with an ESS score of ≥11 in females (OR=2.075, 95% CI=1.163–3.702, *p*=0.013), whereas a PLMI of >15 was less likely to be associated with an ESS score of ≥11 in males (OR=0.711, 95% CI=0.512–0.987, *p*=

Table 3. Results of logistic regression analysis revealing sex interactions with sleep apnea and periodic limb movements during sleep on EDS in patients with OSA (*n*=1,624)

Effect	Sex	ESS score ≥11							
		Crude model				Adjusted model*			
		Interaction *p*	OR	95% CI	*p*	Interaction *p*	OR	95% CI	*p*
AHI ≥30	Male	0.011	1.338	1.068–1.677	0.011	0.013	1.359	1.079–1.713	0.009
	Female		0.644	0.385–1.078	0.094		0.651	0.383–1.106	0.113
PLMI >15	Male	0.003	0.763	0.556–1.046	0.093	0.002	0.711	0.512–0.987	0.041
	Female		2.026	1.158–3.545	0.013		2.075	1.163–3.702	0.013

*Adjusted by BDI score, SHI, and the presence of medical comorbidities.
AHI, apnea-hypopnea index; BDI, Beck Depression Inventory; CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OR, odds ratio; OSA, obstructive sleep apnea; PLMI, periodic limb movements index; SHI, Sleep Hygiene Index.

0.041). The Hosmer–Lemeshow test showed that the model had a good fit (p=0.631). All of the variance inflation factors were <3, and the condition index was 12.5.

DISCUSSION

We found significant sex differences in the relationships between EDS, severe OSA, and PLMS. With regard to the interaction between sex and severe OSA, males but not females were more likely to have EDS when they had severe OSA. These findings are similar to a recent report of the relationship between apnea severity and daytime sleepiness differing between males and females,[14] where each unit increase in ESS score was threefold more strongly related to an increase in AHI in males than in females.[14] In contrast, in the Sleep Heart Health Study (in which 42% of participants were females), the ESS scores did not differ with sex after controlling for AHI.[27] In that study, AHI was significantly correlated with the ESS scores, but no significant moderation of the relationship between them by sex or the presence of nocturnal leg cramps or leg jerks was identified in analyses of the covariance.[27] Similarly, in another recent study (in which 51% of subjects were females), the ESS scores did not differ between males and females after controlling for AHI,[28] and AHI had a significant independent association with daytime sleepiness, with no significant moderation by sex.[28] In addition, we found that EDS was not significantly associated with severe OSA, although an AHI of ≥30 almost reached statistical significance (p=0.078). Some studies have found a significant relationship between EDS and OSA severity,[27,28] but this remains controversial because other studies have not found a strong relationship between EDS and apnea severity in patients with OSA.[9,12] These discrepancies may be due to methodological issues such as differences in the size and in the age and sex distributions of the study populations.

Despite daytime sleepiness not varying with PLMS, we found significant differences in the association between EDS and PLMS depending on sex. Specifically, females with PLMS were sleepier than those without PLMS after controlling for their apnea severity. In contrast, males with PLMS were less sleepy than those without PLMS. The associations between PLMS and daytime sleepiness are inconsistent in the literature. Since PLMS are often accompanied by arousal,[18] their presence may be one of the risk factors for EDS. However, two recent population-based studies did not find that PLMS caused daytime sleepiness regardless of associated arousals.[16,17] It is particularly interesting that some hospital-based studies have found a negative association between PLMS and daytime sleepiness, similar to that observed for males in the present study. A recent Korean study of males with OSA found a significant negative association between EDS and PLMS even after controlling for AHI.[21] Another study of 1,124 adults with OSA (70% of which were males) showed that a PLMI of >5 was inversely associated with sleepiness measured objectively using a multiple sleep latency test, but not with subjectively measured sleepiness (i.e., ESS scores).[29] In contrast, a study of subjects with OSA found that females were more likely to have PLMS than males, particularly among those aged ≤55 years, and that females (but not males) with PLMS had less subjective sleepiness than those without PLMS.[20]

The mechanisms underlying sex differences in the relationships between EDS, severe OSA, and PLMS are unclear. A possible influencing factor is the use of a subjective measure to detect sleepiness. Males and females answer questions about sleepiness differently. Females with OSA are more likely to use various expressions compared to male such as lack of energy, tiredness, or fatigue, to depict their daytime sleepiness.[30] Therefore, using the ESS to detect subjective sleepiness is more likely to identify this in males than in females.[31] However, this does not explain why males were less sleepy than females among the subjects with PLMS in the present study. In a recent study, males with PLMS had a shorter total sleep time and worse sleep architecture than those without PLMS, despite having less-severe OSA.[21] Scofield et al.[32] also reported that those with a PLMI of >15 were much more likely to complain of insomnia than EDS. Decreased sleepiness in males with PLMS despite the presence of significant sleep disturbances raises the possibility that PLMS reflect a neurophysiologic mechanism by which the brain reduces daytime sleepiness.[29] Such an mechanism might explain why PLMS are common in individuals with multiple types of sleep disorders. Another possible mechanism is the influence of untested confounding variables known to be related to PLMS, such as age.[33]

Another possible factor influencing the observed sex differences is the comorbidity of restless legs syndrome (RLS) with PLMS. Similar to the interactions between EDS, PLMS, and sex observed in this study, the Wisconsin Sleep Cohort study found significant interactions between RLS and PLMS with regard to daytime sleepiness measured objectively using a multiple sleep latency test.[16] Specifically, among patients with RLS symptoms, those with PLMS had more daytime sleepiness than those without PLMS, whereas among those without RLS symptoms, those with PLMS had less daytime sleepiness than those without PLMS.[16] Taking into consideration such interactions between RLS and PLMS, and epidemiological data showing that females older than 35 years are twice as likely as males of the same age to have RLS,[29] the findings of the present study indicating increased daytime sleepiness in females with PLMS may partly reflect the interaction between RLS and PLMS. However, most subjects with RLS

rarely complain about daytime sleepiness.[34] Although the findings in the present study are interesting, firm conclusions cannot be drawn because we did not use an objective measure to detect sleepiness or RLS as an independent variable in the analysis.

Some caution is necessary when interpreting our findings. First, our data did not produce evidence for causal or temporal relationships because the study had a cross-sectional design. Second, information was not collected about insomnia, which may influence daytime sleepiness. A recent meta-analysis revealed a high overall prevalence (38%) of insomnia among subjects with OSA.[35] Third, as mentioned above, RLS was not assessed, and so our findings may have been confounded by undiagnosed RLS. Finally, we assessed daytime sleepiness subjectively using the ESS, and the ESS score might not reflect objective sleepiness as measured using the multiple sleep latency test.[36]

In summary, we found significant sex differences in the relationships of subjective daytime sleepiness with severe OSA and PLMS. Specifically, males (but not females) were sleepier when they had severe OSA, whereas females (but not males) were sleepier when they had PLMS.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iDs

Sang-Ahm Lee	https://orcid.org/0000-0002-6743-0545
Kayeong Im	https://orcid.org/0000-0002-4786-096X
Ha-rin Yang	https://orcid.org/0000-0001-7319-6890
Hyo Jae Kim	https://orcid.org/0000-0001-7723-7514

Author Contributions

Conceptualization: Sang-Ahm Lee. Data curation: Kayeong Im, Ha-rin Yang. Formal analysis: Sang-Ahm Lee. Investigation: Sang-Ahm Lee. Methodology: Sang-Ahm Lee. Supervision: Sang-Ahm Lee. Validation: Sang-Ahm Lee. Writing—original draft: Sang-Ahm Lee. Writing—review & editing: Sang-Ahm Lee, Hyo Jae Kim.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

None

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