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ORIGINAL RESEARCH

Clinical Characteristics of Rapid Eye Movement-Related Obstructive Sleep Apnea: An Experience in a Tertiary Medical Center of Taiwan

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Purpose: Obstructive sleep apnea (OSA) is characterized by intermittent hypoxemia and sleep fragmentation. While apnea is pronounced with severe desaturation during rapid eye movement (REM) sleep, REM-related OSA is a distinct phenotype of OSA associated with respiratory disturbances predominantly during REM sleep. In this study, we investigated the clinical features of REM-related OSA in Taiwan.

Patients and Methods: All patients diagnosed with OSA in the Taipei Veterans General Hospital from 2015 to 2017 were analyzed retrospectively and classified into REM-related OSA (REM-OSA) group, non-REM related OSA (NREM-OSA) group, and non-stage specific-OSA group. The clinical demographics, OSA-related symptoms, polysomnography results, and medical comorbidities of the three groups were analyzed.

Results: Among 1331 patients with OSA, 414 (31.1%) were classified as REM-OSA, 808 (60.7%) as NREM-OSA, and 109 (8.2%) as non-stage specific-OSA. After being adjusted for OSA severity, the REM-OSA group was associated with less portion of males, longer desaturation duration, and lower nadir oxygen saturation (SpO_2) compared with the NREM-OSA group in mild and moderate OSA. In moderate OSA, the non-stage specific-OSA group featured more OSA severity and more desaturation compared with the other groups. The Epworth Sleepiness Scale scores and the prevalence of comorbidities did not vary among the REM-OSA, NREM-OSA, and non-stage specific-OSA groups. High REM-AHI/NREM-AHI ratio was associated with young age, female gender, high BMI, and low AHI.

Conclusion: OSA patients with high REM-AHI/NREM-AHI ratio are related to young age, female gender, high BMI, and low AHI. Patients with REM-related OSA presented with longer desaturation duration and lower nadir SpO2 after being adjusted for OSA severity.

Keywords: obstructive sleep apnea, OSA, rapid eye movement, REM, intermittent hypoxia, sleep-disordered breathing

Plain Language Summary

Obstructive sleep apnea (OSA) is a common disorder characterized by snoring and intermittent hypoxemia, and affecting 25% adults. Rapid eye movement (REM) sleep is a unique sleep stage constitutes 20% of sleep duration with diminished muscle activity. This retrospective study found that REM-related OSA accounts for 31% of all OSA patients in Taiwan. REM-related OSA was related to young age, female gender, high BMI, and low AHI. Patients with REM-related OSA presented with longer desaturation duration and lower nadir SpO2 after being adjusted for OSA severity.

Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by snoring, intermittent hypoxemia, and arousals due to recurrent episodes of complete or partial upper airway collapse. OSA is common and occurs in approximately 25% of adults in the US, affecting 34% of men and 17% of women.[1] In Taiwan, the prevalence of snoring is 51.9%, and 2.6%

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Taiwanese have witnessed apnea, estimated by computer-assisted telephone interviews.[2] The risk factors for OSA are old age, male gender, high body mass index (BMI), snoring, and daytime sleepiness.[3] The physiology in different stages of sleep also affects the occurrence of apnea. Rapid eye movement (REM) sleep comprises approximately 20% of normal sleep architecture and is mostly concentrated in the last half of the sleep.[4] During REM, withdrawal of excitatory serotonergic and noradrenergic stimuli to upper airway motor neurons diminishes pharyngeal muscle activity and raises the tendency for upper airway collapse.[4] The disordered breathing events that predominantly manifest during REM sleep, termed as REM-related OSA, constitute 14–36% of patients with OSA by diagnostic polysomnography (PSG) in clinical practice according to different definition criteria.[5–9]

REM-related OSA is a special form of OSA, which is common in female, young adults and associated with low apnea–hypopnea index (AHI).[5,10,11] The pathophysiology of REM-related OSA remains unclear. The vulnerability of REM sleep is probably caused by low respiratory arousal thresholds[12,13] and hypotonia of the pharyngeal dilator muscles,[14–16] which predisposes upper airway obstruction but more stable ventilatory control (measured as lower loop gain) in REM sleep.[17,18] Nonetheless, the trigger factors or pathways to fire these events exclusively during REM sleep are unknown. Patients with REM-related OSA have medical comorbidities, such as diabetes, hypertension, metabolic syndrome, and depressive disorders, which are associated with adverse cardiovascular, metabolic, and neurocognitive dysfunction.[19–23] However, the risk factors, clinical significance, and comorbidities related to this specific OSA entity in Asians are still not well recognized by healthcare professionals in sleep medicine. The aim of this study is to investigate the clinical features of REM-related sleep-disordered breathing (SDB) in Taiwan.

Materials and Methods

This study was approved by the ethics committee of the Taipei Veterans General Hospital (TVGH). All procedures were conducted in accordance with the ethical principles of the institutional review board (IRB) of TVGH, which approved the protocol of the study (approval number 2018–10-003CC). Parental and/or participant consent for reviewing patient medical records was not required by the IRB of TVGH due to the retrospective study design. Patient data confidentiality was covered by compliance with the Declaration of Helsinki. All patients received conventional overnight PSG in the Center of Sleep Medicine of TVGH, from Jan 1st 2015 to Dec 31st 2017 were analyzed retrospectively. The patients had all been referred to the outpatient department of specialized sleep disorder due to suspected OSA-related clinical symptoms. Patients were excluded if they had any of the following: under 20 years old, with known HIV infection, with incomplete Berlin questionnaire or Epworth sleepiness scale (ESS), without sleep-disordered breathing (AHI <5), suspect narcolepsy (REM latency less than 30 minutes), or REM duration less than 30 minutes.[24]

Sleep Study

The PSGs used from 2015 to 2017 included Alice 4, Alice 5, Alice 6 (Philips Respironics, Murrysville, PA, USA), and Embla n7000 (Embla Systems, Inc., Broomfield, CO, USA). The electroencephalogram, electrooculogram, electromyogram, oronasal airflow, chest and abdominal movements, electrocardiogram, snoring, and pulse oximetry for Saturation of Peripheral Oxygen (SpO2) were recorded. All PSG data and results were reviewed manually by Taiwan Society of Sleep Medicine (TSSM) certified specialists. Respiratory events were classified according to standard criteria. Apnea was defined as a decrease of ≥90% in the respiratory signal for at least 10 seconds, and hypopnea was defined as a decrease of 30% to 90% in respiratory signal for at least 10 seconds, followed by an arousal and/or desaturation of ≥3%. AHI was defined as the total number of apneas and hypopneas per hour of sleep and was calculated during REM and non-REM sleep. An overall AHI of 5 to 15 was considered to be diagnostic of mild OSA, and an overall AHI of 15 to 30 was considered to be diagnostic of moderate OSA, and an overall AHI higher than 30 was considered to be diagnostic of severe OSA.

Clinical Evaluation

For all patients, an initial medical history was taken via questionnaire and weight, height, and BMI were measured during physical examination. The patients were interviewed about the presence of snoring, witnessed apneas, nocturia, morning headache and quality of sleep. The degree of daytime hypersomnolence was assessed subjectively in all patients using the

Chinese version[25,26] of Epworth sleepiness scale.[27] Any self-reported history of hypertension, coronary heart disease, diabetes, stroke, or dyslipidemia was recorded as associated comorbidities.

REM-Related OSA, NREM-Related OSA and Non-Stage Specific-OSA Groups

The definition of REM-related OSA (REM-OSA) in our study is according to the strict definition.[28] Those patients with the ratio of AHI during REM sleep (REM-AHI) to AHI during non-REM sleep (NREM-AHI) >2 and NREM-AHI <15/h were classified as REM-related OSA (REM-OSA) group (Figure 1A). Patients with the ratio of REM-AHI/NREM-AHI ≤2 were classified as NREM-OSA group (Figure 1B) and those with REM-AHI/NREM-AHI >2 but NREM-AHI ≥15/h were classified as non-stage specific-OSA group (Figure 1C). REM-isolated OSA (REM-AHI ≥5 and NREM-AHI <5) was also analyzed. The following data were recorded: clinical demographics and symptoms related to OSA, PSG results, and associated medical co-morbidities.

While REM-OSA and NREM-OSA are disorders of OSA spectrum, we also calculate REM-AHI to NREM-AHI ratio of each patient. We then did a logarithmic operation and use log (REM-AHI to NREM-AHI ratio) to explore the relationship between REM-AHI to NREM-AHI ratio and the patient's age, gender, BMI, AHI, and REM-related parameters, such as REM latency, REM duration and REM percentage.

Statistical Analysis

The statistical software SPSS version 22.0 was used for data processing and statistical analysis. Continuous data are examined with Kolmogorov–Smirnov test for normal distribution. While all the continuous variables are non-normally distributed, they are expressed as median (interquartile range). Medians were compared using the Mann–Whitney *U*-test

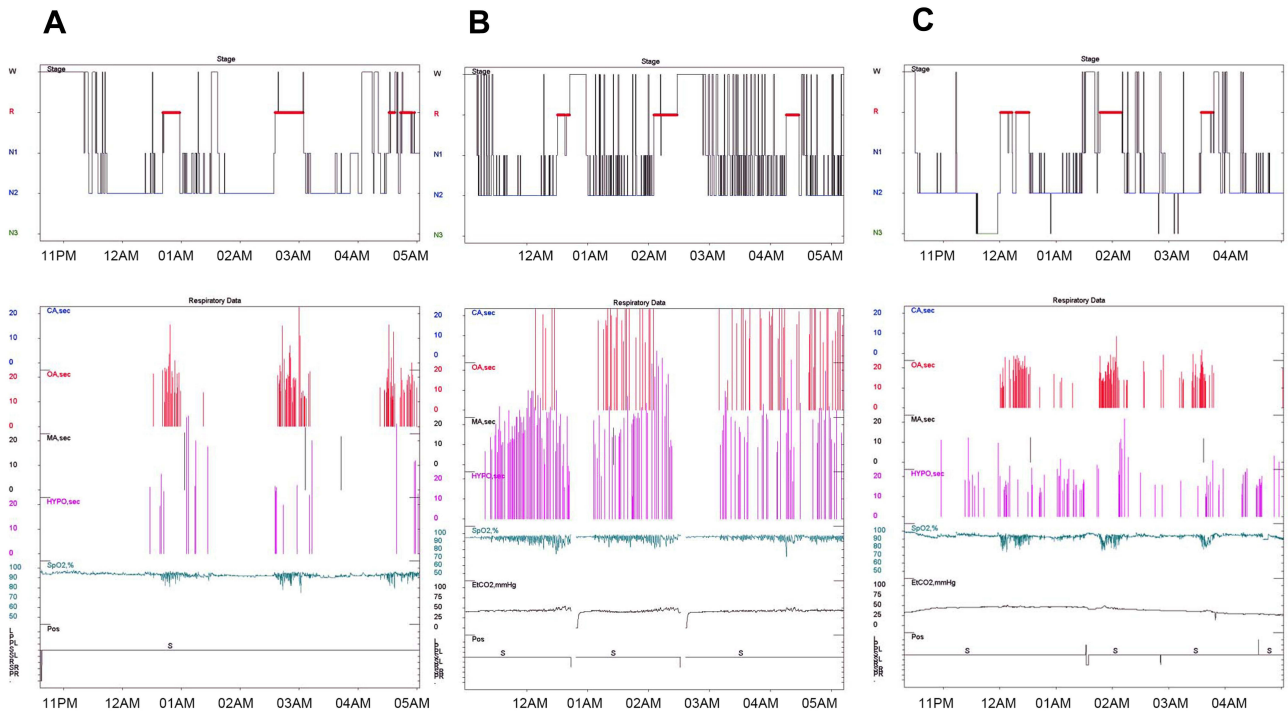

Figure 1 Examples of characteristic graphic summary of overnight polysomnography in REM-OSA, NREM-OSA, and non-stage specific-OSA patient. Upper panel, which shows hypnogram with stages of sleep, including wakefulness (W), REM sleep (red lines) and non-REM sleep (stages N1, N2 and N3). Lower panel, which shows respiratory events with apneas and hypopneas as central, obstructive and mixed. Oximetry, revealing changes in oxygen saturation (SpO_2). Body position with time spent on supine, prone, right side and left side. (**A**) Notice that apneas and hypopneas occur almost exclusively during REM sleep with a clustering of prolonged and severe oxyhemoglobin desaturation. Total AHI = 21.7 events/h, REM-AHI = 69.0 events/h, NREM-AHI = 10.2 events/h, REM-AHI/NREM-AHI > 2. (**B**) Notice that apneas and hypopneas occur extensively during both REM and NREM sleep, not sleep stage-dependent. Total AHI = 42.5 events/h, REM-AHI = 37.3 events/h, NREM-AHI = 42.3 events/h, REM-AHI /NREM-AHI < 2. (**C**) Notice that apneas and hypopneas not only occur predominantly during REM sleep but also arise during NREM sleep. Total AHI = 33.5 events/h, REM-AHI = 95.6 events/h, NREM-AHI = 20.9 events/h, REM-AHI/NREM-AHI > 2.

Abbreviations: AHI, apnea–hypopnea index; NREM, non-rapid eye movement; REM, rapid eye movement.

for two-group comparison. For multiple comparisons, we employed Kruskal–Wallis test to assess the statistical significance of the differences among groups, followed by multiple comparisons with Scheffé method. For the comparison of qualitative variables, the Chi-square test was used. A p-value <0.05 was considered significant for all statistical analyses. Variables with a p-value <0.05 and REM-related parameters, such as REM latency, REM duration and REM percentage were entered into a multivariate linear regression analysis in order to identify those that were independently associated with REM-AHI/NREM-AHI ratio.

Results

From Jan 1st 2015 to Dec 31st 2017, 4458 overnight PSG studies were performed in the sleep center of TVGH, Taipei, Taiwan. Among them, 257 repeated studies, 201 studies of patients <20 years old, 25 studies with incomplete survey, and 912 studies without diagnosis of OSA were excluded. 233 patients with REM latency less than 30 minutes and 1499 patients with REM duration less than 30 minutes were further excluded.

Among 1331 patients with OSA, 414 (31.1%) were classified as REM-OSA, 808 (60.7%) as NREM-OSA, and 109 (8.2%) patients as non-stage specific-OSA (Figure 2). As shown in Table 1, the three groups significantly differed in age, gender, BMI, AHI, OSA severity, REM-AHI, NREM-AHI, REM duration, and REM percentage. The three groups were also differed in percentage of different sleep stages (Table S1). The non-stage specific OSA group was younger than NREM-OSA group. The REM-OSA group was female predominant compared with the NREM-OSA group, and the non-stage specific-OSA group was just in between. The REM-OSA group had lower BMI than the NREM-OSA and

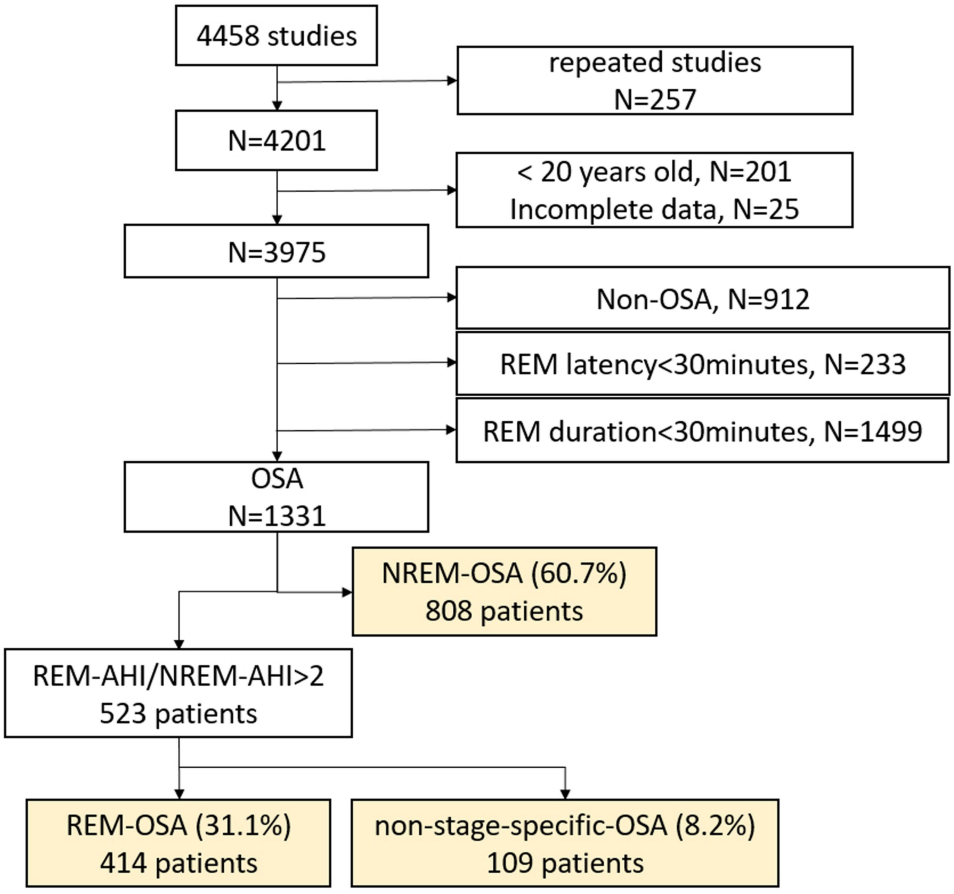

Figure 2 Flow diagram of the study. Enrollment of the patients who underwent polysomnography (N = 4458). After excluding repeated studies (N=257), patients under 20 years old (N=201), incomplete data (N=25), 3975 studies underwent further sleep analysis. Non-OSA patients (N=912), sleep studies with REM latency <30 minutes (N=233), and sleep studies with REM duration <30 minutes (N=1499) were further excluded. Remaining 1331 OSA patients were divided into three groups: REM-OSA group (N = 414), NREM-OSA group (N = 808) and non-stage specific OSA group (N = 109).
Abbreviations: AHI, apnea–hypopnea index; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement.

Table 1 Patient Characteristics

	Total	REM-OSA N = 414	NREM-OSA N = 808	Non-Stage Specific-OSA N = 109	*p* value
Age, yr, median (IQR)	53(42–60)	53(43–61)	53(42–61)	50(40–57)	0.03[c]
Gender (male), N(%)	1058(79.5)	269(65.0)	704(87.1)	85(78.0)	<0.01[a,b,c]
BMI, kg/cm^2, median (IQR)	26.9(24.4–29.9)	26(23.7–29.1)	27.2(24.7–30.2)	28(24.8–30.7)	<0.01[a,b]
Smoker, N (%)	409(30.7)	114(27.5)	259(32.1)	36(33.0)	0.23
ESS, median (IQR)	6(4–9)	6(4–9)	6(4–9)	6(4–9)	0.44
AHI, events/hr, median (IQR)	22.4(11.4–41.7)	10.3(7.4–14.4)	35.3(19–54.2)	26.6(23.6–32.5)	<0.01[a,b]
OSA severity					-
Mild OSA, N (%)		330(79.7)	149(18.4)	0(0)	
Moderate OSA, N (%)		83(20.0)	187(23.1)	75(68.8)	
Severe OSA, N (%)		1(0.3)	472(58.4)	34(31.2)	
REM-AHI, events/hr, median (IQR)	34.6(18.6–53.1)	31.8(23.8–45.3)	32(12.6–53.2)	57.8(49.2–70.8)	<0.01[b,c]
NREM-AHI, events/hr, median (IQR)	20.3(8.2–41.9)	5.6(3.7–9.3)	36.4(20.3–54.8)	20.9(17.9–25.8)	<0.01[a,b,c]
REM latency, min, median (IQR)	87(70–115.5)	84.5(68.4–109.5)	88.5(70.5–119)	86.5(69.8–114.5)	0.13
REM duration, min, median (IQR)	44.7(36.8–54.9)	46.1(38.3–58.1)	43.9(36.5–53.1)	45.8(36.6–54.2)	<0.01[a]
REM percentage, %, median (IQR)	14(11.8–16.9)	14.4(12.2–17.7)	13.8(11.5–16.5)	13.9(12–16.5)	<0.01[a]

Notes: The three groups were compared with Kruskal–Wallis test with Scheffé method for post-hoc analysis and Chi square test with Bonferroni correction for post-hoc analysis. [a]Statistical significance in post-hoc analysis compared REM-OSA and NREM-OSA groups; [b]Statistical significance in post-hoc analysis compared REM-OSA and non-stage specific-OSA groups; [c]Statistical significance in post-hoc analysis compared NREM-OSA and non-stage specific-OSA groups.
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth's sleepiness score; IQR, interquartile range; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement.

non-stage specific-OSA groups. Meanwhile, no significant difference in the Epworth Sleepiness Scale scores for evaluation of clinical hypersomnolence was found between among the three groups. After evaluation of OSA severity by AHI, the REM-OSA group had the lowest AHI, followed by the non-stage specific-OSA group, and the NREM-OSA group had the worst severity. The REM-OSA group was composed mostly of mild (79.7%) and moderate OSA (20.0%) individually. The non-stage specific-OSA group was composed of moderate (68.8%) and severe OSA (31.2%), and the NREM-OSA group was consisted of more severe OSA (58.4%) and less mild-to-moderate OSA (mild: 18.4%, moderate: 23.1%) according to the classification by AHI numbers. Table S2 focused on the REM-isolated OSA (REM-AHI ≥5 but NREM-AHI <5). REM-isolated OSA had more females, less BMI, lower AHI, longer REM duration, and greater REM percentage compared with the other OSA patients.

A subgroup analysis according to the different levels of OSA severity was performed to minimize the effects of AHI. Among the patients with mild OSA, the REM-OSA group had more females, less AHI, longer desaturation duration, and lower nadir SpO_2 compared with the NREM-OSA group (Table 2). The characteristics of patients with moderate OSA are shown in Table 3. Compared with the NREM-OSA group, the REM-OSA group had more females, lower AHI, less desaturation index, longer desaturation duration, and lower nadir SpO_2. Compared with the non-stage specific-OSA group, the REM-OSA group had less AHI and less desaturation index, but without different desaturation duration and nadir SpO_2. The NREM-OSA group was older and had lower AHI, less desaturation index, shorter desaturation duration, and higher nadir SpO_2 than the non-stage specific-OSA group. Prevalence of comorbidities, including hypertension, diabetes mellitus, heart disease, stroke, hyperlipidemia, anxiety, and depression, did not vary among the REM-OSA, NREM-OSA, and non-stage specific-OSA groups when analyzed according to OSA severity. Patients with severe OSA were analyzed in Table 4. Only 1 patient with severe OSA was in REM-OSA group, and the characteristics were shown in Table S3. Most patients with severe OSA were the non-stage specific-OSA and NREM-OSA groups in accordance with strict criteria, which are shown in Table 4. The severe NREM-OSA group had more males, higher AHI, and higher degree of oxygen desaturation indices compared with the non-stage specific-OSA group. The BMI of the non-stage specific-OSA group was comparably as high as that of the NREM-OSA group with severe OSA.

To further explore the relationship between REM-specific SDB and patient characteristics including age, AHI, and BMI, we prepared a scatter plot between those parameters according to log (REM-AHI/NREM-AHI ratio) in Figure 3.

Table 2 Demographics of REM-OSA Patients and NREM-OSA in Mild OSA Patients

	REM N = 330	NREM N = 149	*p* value
Age, yr, median (IQR)	53(42–61)	53(41.5–62)	0.57
Gender (male), N (%)	209(63.5)	118(79.2)	<0.01
BMI, kg/cm^2, median (IQR)	25.9(23.6–28.9)	25.2(23.5–28.1)	0.11
Smoker, N (%)	90(27.4)	43(28.9)	0.74
ESS, median (IQR)	6(4–9)	6(4–8)	0.99
AHI, events/hr, median (IQR)	9.2(6.9–11.7)	9.8(7.2–12.5)	0.06
REM-AHI, events/hr, median (IQR)	28.8(21.6–37.3)	7.2(2.5–11.3)	<0.01
NREM-AHI, events/hr, median (IQR)	4.8(3.4–6.8)	10.6(7.9–12.9)	<0.01
REM latency, min, median (IQR)	84(68.5–110)	86.5(71.5–118)	0.24
REM duration, min, median (IQR)	46.1(38.3–57.8)	45.5(36.5–55.6)	0.26
REM percentage, %, median (IQR)	14.3(12.2–17.1)	14.1(12.0–17.7)	0.33
Desaturation index, events/hr, median (IQR)	7.5(5.6–10.4)	8.6(5.7–10.9)	0.10
SpO2<90%, min, median (IQR)	2.5(0.7–5.6)	1(0.1–3.2)	<0.01
Nadir SpO2, %, median (IQR)	83(80–87)	86(83.5–89)	<0.01
Hypertension, N (%)	98(29.8)	48(32.2)	0.59
Diabetes, N (%)	34(10.3)	18(12.1)	0.57
Heart disease, N (%)	33(10.0)	13(8.7)	0.65
Stroke, N (%)	11(3.3)	5(3.4)	1.00
Hyperlipidemia, N (%)	102(31.0)	46(30.9)	0.98
Anxiety, N (%)	55(16.7)	28(18.8)	0.58
Depression, N (%)	18(5.5)	8(5.4)	0.96

Note: The two groups were compared with Mann–Whitney *U*-test and Chi square test.
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth's sleepiness score; IQR, interquartile range; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement.

Table 3 Demographics of REM-OSA Patients and NREM-OSA in Moderate OSA Patients

	REM N = 83	NREM N = 187	Non-Stage Specific N = 75	*p* value
Age, yr, median (IQR)	53(46–59)	55(46–64)	50(40–58)	0.02[c]
Gender (male), N (%)	58(69.9)	157(84.0)	61(81.3)	0.03[a]
BMI, kg/cm^2, median (IQR)	26.2(24.1–30.5)	26(23.8–28.6)	27.6(24.2–29.8)	0.09
Smoker, N (%)	23(27.7)	55(29.4)	27(36.0)	0.48
ESS, median (IQR)	6(4–9)	6(4–8)	7(4–9)	0.62
AHI, events/hr, median (IQR)	17.9(16.6–19.2)	22.6(18.6–26)	24.4(22.4–26.8)	<0.01[a,b,c]
REM-AHI, events/hr, median (IQR)	50(41.3–58.1)	18.8(9.6–27.3)	53.6(46.4–60)	<0.01[a,c]
NREM-AHI, events/hr, median (IQR)	11.7(10.3–13.7)	23.3(19.2–26.2)	18.7(16.7–21.1)	<0.01[a,b,c]
REM latency, min, median (IQR)	85(67–106.5)	85.5(67.5–114)	85(71–114.5)	0.98
REM duration, min, median (IQR)	46.8(38.5–62)	44.9(36.4–56.7)	44.9(35.7–52.6)	0.13
REM percentage, %, median (IQR)	14.8(12.1–18.7)	14.4(12.1–17.8)	13.9(12.1–16.2)	0.17
Desaturation index, events/hr, median (IQR)	16(13.8–18)	19.1(16.2–23.4)	22(19.3–24.7)	<0.01[a,b,c]
SpO2<90%, min, median (IQR)	8.4(4.5–18.8)	6.2(2.1–13.3)	12.4(5.9–19)	<0.01[a,c]
Nadir SpO2, %, median (IQR)	79(73–82)	82(79–85)	77(70–81)	<0.01[a,c]
Hypertension, N (%)	29(34.9)	71(38.0)	23(30.7)	0.53
Diabetes, N (%)	12(14.5)	29(15.5)	9(12.0)	0.77
Heart disease, N (%)	10(12.0)	22(11.8)	11(14.7)	0.81
Stroke, N (%)	3(3.6)	5(2.7)	4(5.3)	0.57
Hyperlipidemia, N (%)	27(32.5)	59(31.6)	19(25.3)	0.55
Anxiety, N (%)	18(21.7)	30(16.0)	11(14.7)	0.43
Depression, N (%)	11(13.3)	13(7.0)	4(5.3)	0.13

Notes: The three groups were compared with Kruskal–Wallis test with Scheffé method for post-hoc analysis and Chi square test with Bonferroni correction for post-hoc analysis. [a]Statistical significance in post-hoc analysis compared REM-OSA and NREM-OSA groups; [b]Statistical significance in post-hoc analysis compared REM-OSA and non-stage specific-OSA groups; [c]Statistical significance in post-hoc analysis compared NREM-OSA and non-stage specific-OSA groups.
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth's sleepiness score; IQR, interquartile range; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement.

Table 4 Demographics of REM-OSA Patients and NREM-OSA in Severe OSA Patients

	NREM N = 472	Non-Stage Specific N = 34	*p* value
Age, yr, median (IQR)	52(42–59)	50(39.8–54.3)	0.17
Gender (male), N (%)	429(90.9)	24(70.6)	<0.01
BMI, kg/cm^2, median (IQR)	28.3(25.9–31.2)	28.4(26.7–31.7)	0.50
Smoker, N (%)	161(34.1)	9(26.5)	0.36
ESS, median (IQR)	7(4–10)	5.5(4–9)	0.30
AHI, events/hr, median (IQR)	50.8(40.2–66.9)	35.3(32.7–42.5)	<0.01
REM-AHI, events/hr, median (IQR)	50.2(34.9–63.3)	75.3(70.1–90.6)	<0.01
NREM-AHI, events/hr, median (IQR)	50.9(39.8–68.7)	28.5(26.5–35.4)	<0.01
REM latency, min, median (IQR)	91(70.5–121.3)	96.5(68.3–115.9)	0.97
REM duration, min, median (IQR)	43.3(36.6–51.4)	46(36.7–56.8)	0.34
REM percentage, %, median (IQR)	13.5(11.2–15.7)	14.0(11.6–17.4)	0.31
Desaturation index, events/hr, median (IQR)	46.7(35.2–63.2)	33.7(30.7–39.6)	<0.01
SpO2<90%, min, median (IQR)	40.1(16.1–83.5)	22.2(13.7–31.1)	<0.01
Nadir SpO2, %, median (IQR)	73(64–79)	76(70.8–81)	0.04
Hypertension, N (%)	181(38.3)	10(29.4)	0.30
Diabetes, N (%)	53(11.2)	3(8.8)	0.67
Heart disease, N (%)	46(9.7)	5(14.7)	0.35
Stroke, N (%)	16(3.4)	2(5.9)	0.45
Hyperlipidemia, N (%)	152(32.2)	9(26.5)	0.49
Anxiety, N (%)	65(13.8)	7(20.6)	0.27
Depression, N (%)	20(4.2)	5(14.7)	0.01

Note: The two groups were compared with Mann–Whitney *U*-test and Chi square test.
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth's sleepiness score; IQR, interquartile range; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement.

The REM-AHI/NREM-AHI ratio increased as age decreased (Figure 3A), BMI increased (Figure 3B), and AHI decreased (Figure 3C) from the plotting of the figure A multivariate linear regression was performed to find the relationship between log (REM-AHI/NREM-AHI) and the four basic characteristics (age, gender, AHI, and BMI) and three REM-related parameters (REM latency, REM duration, and REM percentage) in Table 5. The high REM-AHI /NREM-AHI ratio in our patients with OSA was associated with young age, female gender, high BMI, and low AHI.

Discussion

OSA is a prevalent systemic disease characterized by intermittent hypoxia and sleep fragmentation, causing increased oxidative stress, inflammation, and sympathetic activity and substantially leading to cardiorespiratory, metabolic, and neuropsychiatric illness. REM-related OSA is a distinct phenotype that is underestimated and undertreated because of less OSA severity by AHI and insufficient continuous positive airway pressure (CPAP) use to cover the early morning hours, which consist of more REM sleep periods.[11] This retrospective study was conducted in a TSSM-certified sleep center in a tertiary medical center and also the first to investigate the clinical aspects about REM-related OSA in Taiwan. The overall REM-OSA group was female predominant and with less BMI and less OSA severity compared with the NREM-OSA group. After being adjusted for OSA severity, the REM-OSA group was associated with female gender, longer desaturation duration, and lower nadir SpO_2 compared with the NREM-OSA group in mild and moderate OSA. The non-stage specific-OSA group shared the similar characteristic clustering of severe desaturation confined mainly to REM sleep but had greater NREM-AHI, greater OSA severity, and greater desaturation index compared with the REM-OSA group. In our patients with OSA, high REM-AHI/NREM-AHI ratio was associated with young age, female gender, high BMI, and low AHI.

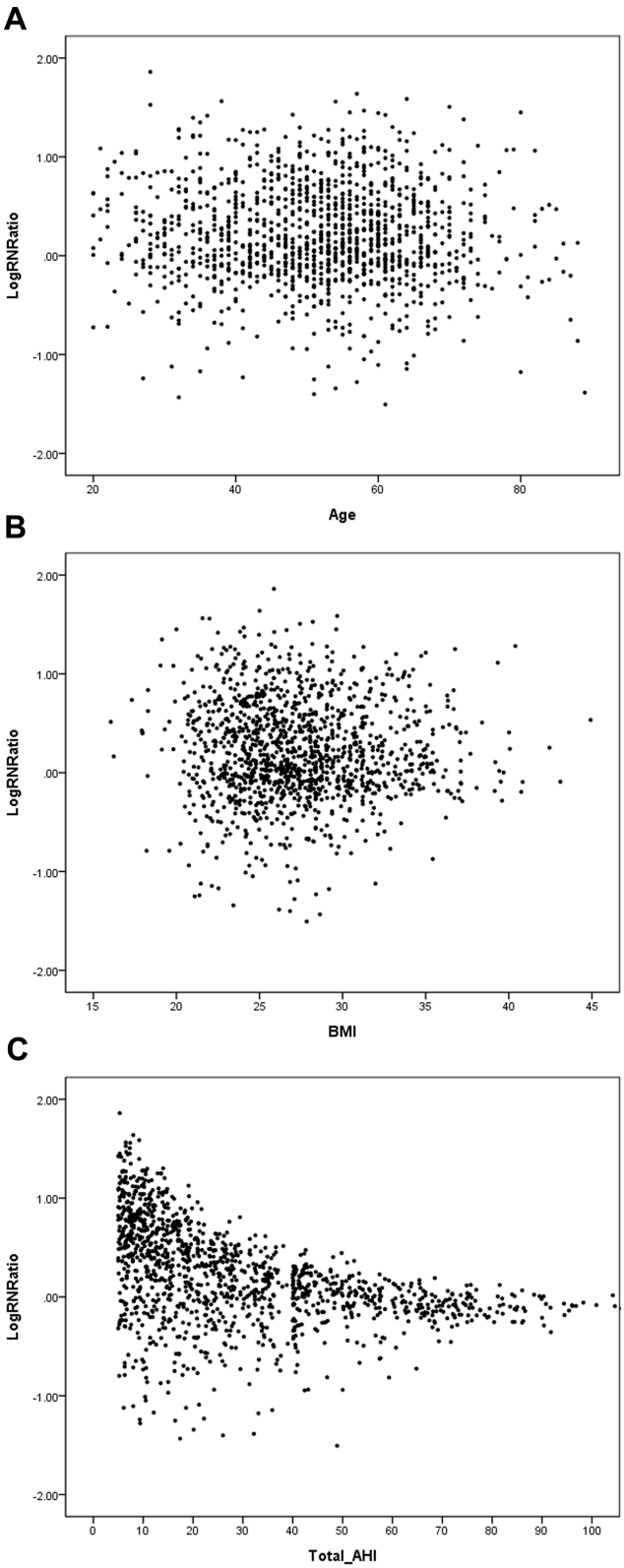

Figure 3 Relation between log (REM-AHI to NREM-AHI ratio) and age, BMI and AHI. The scatter plot showed the negative correlation between RNRatio and age (**A**), positive correlation between RNRatio and BMI (**B**), and negative correlation between RNRatio and AHI (**C**).
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; NREM, non-rapid eye movement; REM, rapid eye movement; RNRatio, REM-AHI to NREM-AHI ratio.

Table 5 Risk Factors Associated with Log(REM-AHI to NREM-AHI Ratio)

	B	Standard Error	*p* value
Age	−0.004	0.001	<0.01
Gender (male), (male: 1, female: 2)	0.304	0.031	<0.01
BMI	0.014	0.003	<0.01
AHI	−0.008	0.001	<0.01
REM latency	0.000	0.000	0.14
REM duration	0.001	0.001	0.32
REM percentage	−0.001	0.004	0.72

Notes: The high REM-AHI to NREM-AHI ratio was associated to young age, female gender, high BMI, and low AHI.
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; NREM, non-rapid eye movement; REM, rapid eye movement.

In the studies investigating REM-related OSA, the definition and prevalence vary because of the different sample characteristics and inconsistent criteria used to define REM-related OSA.[5–7,29–31] In our study, the definition of REM-related OSA is REM-AHI/NREM-AHI >2 and NREM-AHI <15 as used in most of the previous studies.[6,7,29] The definition in our study is a modified edition to the broad definition (REM-AHI/NREM-AHI >2) of REM-related OSA, which is termed as REM-specific SDB.[5] Unlike the traditional binary definition, NREM-AHI <15 is included in REM-OSA to minimize the mixed effect of NREM-OSA and a non-stage specific-OSA group is established for those with NREM-AHI ≥15. In our study, the proportion of REM-related OSA is 31.1% of all patients with OSA, which is higher than that in a Jordan study[28] even though our definition is stricter than the broad definition. The non-stage specific-OSA group accounts for 8.2% in all patients with OSA, indicating that approximately 2/5 (39.3%) patients with OSA have REM-AHI/NREM-AHI ratio >2 and 1/4 of patients with REM-specific SDB have NREM-AHI ≥15. The modified definition helps us distinguish the effect of OSA on the REM and NREM stages individually in patients with moderate OSA. A large number of patients (N = 109) were diagnosed with non-stage specific-OSA. To further focus on the REM effect, we also did an analysis for REM-isolated OSA, which featured the same trend about more females, younger age and lower AHI.

The REM-related OSA group presented with less BMI and less OSA severity in the whole OSA group, which is consistent with previous studies using the strict definition criteria.[32,33] However, the less BMI was due to selection bias as the patients with NREM-AHI ≥15 were classified as the non-stage specific-OSA group, and the BMI did not differ significantly after adjusted with OSA severity. The regression model of log (REM-AHI/NREM-AHI) also showed the positive effect of BMI because obesity would have an accentuated effect to collapse the upper airways during REM sleep.[30] Apart from BMI, the AHI was also affected by selection bias. In mild OSA, no significant difference in AHI was found between the REM-OSA and NREM-OSA groups. In moderate OSA, the REM-OSA group had lower AHI than the NREM-OSA group, whereas the non-stage specific-OSA group had higher AHI than the NREM-OSA group. The relationship between REM-AHI/NREM-AHI ratio and clinical features, such as age, gender, BMI, and AHI, was further explored. A logarithmic transformation to REM-AHI/NREM-AHI was performed for the first time in this study to balance the effect of REM-AHI and NREM-AHI statistically and visually. Results showed that high REM-AHI/NREM-AHI ratio was related to young age, female gender, high BMI, and low AHI.

In the aspect of pathophysiology, the REM stage is characterized by decreased genioglossus muscle tone due to the cholinergic-mediated suppression of the hypoglossal nerve and leads to vulnerability of upper airway obstruction.[4,15,16] In our study, REM-OSA was more common in women, which is compatible with previous studies.[29,30] Women have greater genioglossus activity than men during awake and NREM sleep, and this protective mechanism is further reduced during REM sleep partially caused by hormonal changes.[29] In recent clinical results, patients with REM-OSA demonstrated a significantly more collapsible upper airway, and withdraw of neural ventilatory drive,[34] whereas patients with NREM-OSA had more unstable ventilatory control ability.[18] Therefore, REM-OSA features clustering of great degrees of severe hypoxemia, ventilator drive withdrawal and high levels of sympathetic activity predominantly during REM sleep because of

reduced muscle tone and response to hypercapnic and hypoxic respiratory drive during REM sleep.[4] In our study, the REM-OSA group had longer sleep time of SpO_2 below 90% and lower nadir SpO_2 than the NREM-OSA group in patients with mild-to-moderate OSA. In addition, the non-stage specific-OSA group had longer desaturation duration and lower nadir SpO_2 in patients with moderate OSA. This result agrees with previous findings[35–37] and reflects the adverse impact of clustered obstructive events during REM sleep on the severity of hypoxemia.[35] Recently, growing evidence has emphasized that the distribution of hypoxic respiratory events, the depth and duration of desaturation, and the level of sympathetic activity should be considered as useful clinical parameters other than AHI to evaluate the severity and outcomes of OSA.[28,38,39] In addition, arousals and interruption of REM sleep may lead to deleterious effects on cognition, emotion, memory consolidation, and augmentation, which also cannot be assessed by AHI.[4] We also presented the relationship between different types of OSA and self-reported ESS score and sleep-related comorbidities, including hypertension, diabetes, heart disease, stroke, hyperlipidemia, anxiety, and depression, to explore the clinical influence in severe intermittent hypoxemia and active sympathetic activity. In patients with mild OSA, the ESS score and prevalence of these comorbidities did not show significant difference, whereas AHI remained the same in both groups. Although the AHI was lower in the patients with REM-related OSA in the moderate OSA group, the ESS score and prevalence of these comorbidities also did not show significant differences among the REM-OSA, NREM-OSA, and non-stage specific-OSA groups in moderate OSA. This result may imply the higher destruction power to health status and quality of life in REM-related OSA, which is similar to previous results.[40–42] Depression in severe OSA is the only comorbidity that differed statistically between non-stage specific OSA and NREM OSA groups. However, the relationship between depression and REM-OSA is controversial.[43,44] Further prospective study is warranted.

This study has several limitations because of its retrospective nature. Unlike cross-sectional survey, selection bias always exists and may also occur. This study was conducted in a single tertiary medical center, but the patients were grouped according to OSA severity to minimize the effect. Second, the ESS score and medical comorbidities were recorded via a self-reported questionnaire but not clinically proven. This result might be influenced by self-cognition to the illness or underestimate the prevalence of OSA-related comorbidities. Although we hold the sedatives before sleep studies as the protocol, the background drug profile was not recorded. Future prospective study and follow-up of REM-OSA patients compared with NREM-OSA and non-stage specific-OSA patients might raise further evidence on whether or not REM-related OSA is a special clinical entity that is mandatory for aggressive management with CPAP machine or other therapeutic modalities.

Conclusion

High REM-AHI/NREM-AHI ratio was associated with young age, female gender, high BMI, and low AHI in our OSA patients. REM-related OSA patients presented with intermittently more severe breathing events during REM sleep, resulting in longer desaturation duration and lower nadir oxygen saturation. This disorder may strongly impact the OSA-related medical comorbidities due to upregulation of hypoxia-induced oxidative stress and inflammation and disturbance of sympathetic activities and autonomic nervous system even in low AHI.

Data Sharing Statement

The unpublished data cannot be shared due to IRB restriction and hospital policies.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they know of no conflicts of interest in relation to this paper.

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