

# Clinical phenotypes of patients with obstructive sleep apnea-hypopnea syndrome: a cluster analysis

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*To the Editor:* Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common sleep-disordered breathing disease with a range of harmful sequelae. As a syndrome related to multiple systems,<sup>[1]</sup> the clinical presentation of OSAHS is characterized by a large heterogeneity. At the World Sleep 2019 conference, a series of cluster analyses on the Icelandic sleep apnea cohort<sup>[2]</sup> were introduced in detail. However, data from China are missing due to less relevant studies. Furthermore, although the relationship between OSAHS and cognitive impairment was confirmed in the 1980s, all variables assessing cognitive function have not yet been explored.

This retrospective study was performed using data from consecutive patients diagnosed with OSAHS at the Sleeping Center of the Second Affiliated Hospital of Soochow University between January 2014 and December 2018. This study protocol was approved by the ethics committee of the Second Affiliated Hospital of Soochow University (No. JD-LK-2018-004-02). All the participants provided written informed consent.

Patients who were diagnosed with OSAHS (apnea-hypopnea index [AHI] >5 events/h) and could accurately fill in the Epworth Sleeping Scale (ESS) and Montreal Cognitive Assessment (MoCA) scale were included except those who had serious central nervous system diseases or received continuous positive pressure ventilation and other treatments (prescribed drugs that might affect sleep). Finally, 1044 patients (aged 14–83 years) were enrolled in the study.

Fourteen variables, including demographic characteristics (sex, age, body mass index, smoking status, and drinking status), symptoms, comorbidities, ESS, and MoCA scores were selected for analysis. ESS is a method for measuring daytime sleepiness. MoCA is a 30-point test that is

commonly used to detect mild cognitive impairment. According to the standard of the World Health Organization,<sup>[3]</sup> a smoker is someone who, at the time of the survey, smokes any tobacco product either daily or occasionally; the man who consumed at least one alcoholic drink of any kind over the past year was defined as a drinker.<sup>[4]</sup> Besides the three typical symptoms, including snoring, breathing pauses at sleep, and sudden awakening due to sleep apnea, other symptoms were sorted into three domains: nocturnal symptoms (increased frequency of night urine, leg movement during sleep, dream, nightmare, and somnambulism), daytime symptoms (fatigue upon awaking, headache upon awaking, and thirst upon awaking), and insomnia-related symptoms (insomnia, difficulty falling asleep, and early awakening). As long as the participant had one of the symptoms listed in parentheses for each indicator, a score was recorded. The results of the data for comorbidities were used to obtain the total score. When a patient had a complicated disease (including diabetes, hypertension, coronary heart disease, arrhythmia, chronic obstructive pulmonary diseases, gastroesophageal reflux, asthma, hyperthyroidism, hypothyroidism, liver disease, and transient ischemic attack), he received an additional point.

The aforementioned information for all patients at the time of the first visit was obtained under the guidance of the sleep center staff. While the patients remained in the sleep laboratory, overnight monitoring (Alice 6, Philips, Pittsburgh, PA, USA; E Series, Compumedics, Abbotsford, VIC, Australia) was performed. The examination was considered to be good if at least 4 h of registration was recorded. After monitoring, all data were automatically played back by a computer and corrected by professional sleep respiratory doctors.

Data analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). Due to

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more binary variables, a two-step clustering analysis was used to generate clusters. This approach is a clustering algorithm used in SPSS Modeler. After subgroups were identified, the normality of the continuous variables was tested using the Kolmogorov-Smirnov test and the homogeneity of variance was tested using the Levene test. Continuous variables with normal distribution were presented as mean  $\pm$  standard deviation and those with skewed distribution as median ( $Q_1$ ,  $Q_3$ ), while categorical variables were expressed as numbers (percentages). A one-way analysis of variance was applied for normally distributed continuous variables, Kruskal-Wallis  $H$  test was used for non-normally distributed continuous variables, and Chi-square test or Fisher exact test was used for categorical variables. A  $P$  value of  $< 0.05$  indicated a statistically significant difference.

Four distinct clusters were identified based on these clinical characteristics. Cluster 1 was the “Classic group” ( $n = 318$ ), consisting of 30.5% of the entire cases. The members of this cluster had the highest ESS score among the four clusters. They also had the highest likelihood of presenting with three typical obstructive sleep apnea (OSA) symptoms, such as snoring (318/318, 100%), breathing pauses at sleep (318/318, 100%), and sudden awakening due to sleep apnea (135/318, 42.5%). Cluster 2 was the

“minimally symptomatic group” ( $n = 231$ ), consisting of 22.1% of the entire cases. Patients in this group lacked typical OSA symptoms and had the lowest ESS score. Cluster 3 was the “cognitive impairment group” ( $n = 123$ ), consisting of 11.8% of all cases. This group had the lowest MoCA score. Cluster 4 was the “daytime symptomatic group” ( $n = 372$ ), consisting of 35.6% of the entire cases. They had the maximum symptoms upon waking up in the morning, such as fatigue, headache, and thirst. When comparing the polysomnographic parameters between different clusters, a significant difference was found in AHI ( $H = 54.200$ ,  $P < 0.001$ ), oxygen desaturation index ( $H = 50.736$ ,  $P < 0.001$ ), percentage of total sleep time spent below 90% oxygen saturation ( $H = 65.938$ ,  $P < 0.001$ ), lowest oxygen saturation ( $H = 47.849$ ,  $P < 0.001$ ), longest apnea time ( $H = 64.964$ ,  $P < 0.001$ ), respiratory effort-related arousal ( $H = 56.641$ ,  $P < 0.001$ ), arousal index ( $H = 10.756$ ,  $P = 0.013$ ), and percentage of slow-wave sleep ( $H = 42.362$ ,  $P < 0.001$ ). No significant differences in polysomnographic parameters between clusters 1 and 4 were found. Nevertheless, there were significant differences in MoCA scores ( $P = 0.004$ ), smoking ( $P < 0.001$ ) and drinking ( $P < 0.001$ ) between cluster 1 and 4. The differences in clinical characteristics and polysomnographic parameters among clusters are summarized in Table 1.

**Table 1: Comparison of clinical characteristics and polysomnographic parameters among different clusters of patients with obstructive sleep apnea-hypopnea syndrome.**

Items	Cluster 1 ( $n = 318$ )	Cluster 2 ( $n = 231$ )	Cluster 3 ( $n = 123$ )	Cluster 4 ( $n = 372$ )	Statistics	$P$
Population characteristics						
Age (year)	41.85 $\pm$ 10.67	41.12 $\pm$ 12.93	50.10 $\pm$ 14.21	41.62 $\pm$ 11.10	$F = 19.225$	$< 0.001$
Sex (female/male)	0/318	0/231	109/14	0/372	–	$< 0.001$
BMI ( $\text{kg}/\text{m}^2$ )	27.58 $\pm$ 3.23	27.62 $\pm$ 4.84	26.35 $\pm$ 3.69	27.61 $\pm$ 3.66	$F = 3.830$	0.010
Smoking (no/yes)	104/214	128/103	122/1	219/153	–	$< 0.001$
Drinking (no/yes)	0/318	140/91	119/4	372/0	–	$< 0.001$
Clinical presentations						
Snoring (no/yes)	0/318	8/223	4/119	2/370	–	$< 0.001$
Breathing pauses (no/yes)	0/318	231/0	38/85	0/372	–	$< 0.001$
Apnea awakening (no/yes)	183/135	207/24	74/49	243/129	–	$< 0.001$
Daytime symptoms	1 (1, 2)	1 (0, 2)	1 (0, 2)	1 (1, 2)	$H = 17.011$	0.001
Nocturnal symptoms	1 (1, 2)	1 (0, 2)	2 (1, 2)	1 (1, 2)	$H = 6.405$	0.093
Insomnia-related symptoms	1 (0, 1)	1 (0, 1)	1 (1, 2)	1 (0, 1)	$H = 12.908$	0.005
Comorbidities	1 (0, 1)	0 (0, 1)	1 (0, 1)	0 (0, 1)	$H = 8.292$	0.040
Score						
ESS	10 (6, 14)	8 (5, 12)	9 (4, 14)	9 (5, 14)	$H = 18.592$	$< 0.001$
MoCA	27 (25, 28)	27 (25, 28)	26 (22, 28)	27 (26, 28)	$H = 31.363$	$< 0.001$
PSG parameters						
AHI (events/h)	45.8 (24.5, 65.9)	30.3 (13.1, 55.3)	23.2 (10.7, 47.6)	44.6 (23.4, 66.2)	$H = 54.200$	$< 0.001$
ODI (events/h)	42.2 (19.9, 62.7)	27.2 (11.3, 51.3)	19.2 (9.3, 47.0)	41.8 (21.1, 61.9)	$H = 50.736$	$< 0.001$
TS90% (%)	13.7 (3.8, 37.3)	5.4 (0.9, 19.7)	3.6 (0.8, 15.1)	15.9 (3.8, 35.7)	$H = 65.938$	$< 0.001$
LSaO <sub>2</sub> (%)	75 (65, 82)	80 (71, 85)	80 (71, 86)	74 (67, 82)	$H = 47.849$	$< 0.001$
LAT (s)	65.0 (52.6, 81.0)	56.0 (43.0, 74.0)	50.0 (39.0, 62.0)	65.3 (50.0, 80.4)	$H = 64.964$	$< 0.001$
RERA (events/h)	21.5 (7.0, 41.3)	10.6 (3.5, 28.0)	6.4 (2.3, 20.2)	19.8 (6.7, 37.5)	$H = 56.641$	$< 0.001$
AI (events/h)	29 (20, 42)	27 (17, 38)	24 (16, 36)	28 (19, 38)	$H = 10.756$	0.013
SWS% (%)	8.9 (2.4, 15.8)	13.3 (7.2, 19.2)	16.1 (9.7, 20.4)	10.9 (4.2, 16.9)	$H = 42.362$	$< 0.001$

Data were presented as mean  $\pm$  standard deviation,  $n/n$  or median ( $Q_1$ ,  $Q_3$ ). AHI: Apnea-hypopnea index; AI: Arousal index; BMI: Body mass index; ESS: Epworth sleepiness scale; LAT: Longest apnea time; LSaO<sub>2</sub>: Lowest arterial oxygen saturation; MoCA: Montreal Cognitive Assessment; ODI: Oxygen desaturation index; PSG: Polysomnography; RERA: Respiratory effort related arousal; SWS%: Percentage of slow-wave sleep; TS90%: Percentage of the total sleep time spent below 90% oxygen saturation.

This study successfully verified the clinical phenotypes in patients with OSAHS. Based on the impact of cognitive impairment on the quality of life and mortality,<sup>[5]</sup> the cognitive status was evaluated using MoCA in addition to conventional population characteristics and common clinical presentations.

Different from previous studies, this study found four subgroups with a distinct pattern of symptoms among patients with OSAHS in Southern Jiangsu of China. Nearly 30% of the patients with OSAHS had cognitive impairment (312 with the MoCA score below normal). The existence of the subgroup of cognitive impairment (cluster 3) was confirmed in the OSAHS population for the first time. A majority of patients in this group were women having the most insomnia-related and nocturnal symptoms.

Consistent with the previous findings,<sup>[2]</sup> patients were divided into a classic group (cluster 1) and a minimally symptomatic group (cluster 2). Patients in the minimally symptomatic group reported a better ESS score and lower comorbidity. This finding supported the symptom status as a key predictor of quality of life.

The last group was named the daytime symptom group. The members in cluster 4 were much more likely to feel fatigue, have a headache, and feel thirsty upon waking up and were characterized by the fewest comorbidities and the highest MoCA score. Patients in this group had good living habits, and the symptoms were more prominent during the daytime. All these observations prompted patients to see a doctor in time.

The severity of OSAHS condition was judged according to AHI in clinical practice; yet, no differences in polysomnographic parameters were found between clusters 1 and 4. Nevertheless, remarkable differences were noted in cognitive impairment. Patients in cluster 3 had the best polysomnographic results, whereas they had the lowest MoCA score and the maximum comorbidities. These findings led to the conclusion that the AHI did not reflect the clinical consequences.

In addition, the psychological and physiological symptoms of OSAHS are sex-specific.<sup>[6]</sup> The members of cluster 3 were all women. Previous studies<sup>[7]</sup> suggested that changing estrogen levels could affect the brain systems involved in mood and cognition. White matter injury that occurred more often in female patients than in male patients might be associated with more common cognitive impairment in women.<sup>[8]</sup> The risk of cognitive impairment was higher in middle-aged to elderly patients with OSAHS than in young patients with the same severity. The average age (51 years) of patients in cluster 3 was significantly higher than that in the other three clusters. These women were in the peri-menopausal period accompanied by hot

flashes, night sweating, nocturnal urine, and other symptoms that disturbed sleep.

In summary, the study provided new evidence that clinical heterogeneity and cognitive impairment form a special subgroup of OSAHS. Symptom assessment is very important to identify OSAHS and the severity of the disease. The cognitive function should be considered as a routine evaluation item for patients with OSAHS, especially women.

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### Conflicts of interest

None.

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