

# Recognizable Clinical Subtypes of Obstructive Sleep Apnea After Ischemic Stroke: A Cluster Analysis

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**Background and Purpose:** Obstructive sleep apnea (OSA) increases risk of stroke recurrence and mortality in ischemic stroke patients. However, equivocal treatment effects warrant further categorization of post-stroke OSA for risk stratification and individualized treatment planning.

**Methods:** The study recruited 232 ischemic stroke patients with moderate-to-severe OSA admitted for inpatient rehabilitation consecutively. Latent class analysis was performed based on sex, age, smoking, daytime sleepiness, depression, obesity, sedative use, atrial fibrillation, diabetes, dyslipidemia, hypertension, recurrent stroke and dysphagia. The augmentation index, a marker of arterial stiffness, was measured by applanation tonometry.

**Results:** A three-cluster model provided the best fit. Cluster 1 (n=84, 36.2%) was older in age, predominantly female, with the highest hypopnea index and prevalence of atrial fibrillation. Moreover, patients in Cluster 1 had significantly higher augmentation index than those in Cluster 2. Cluster 2 patients (N=80, 34.5%) were of older age, predominantly male, with the highest prevalence of depression, the lowest prevalence of hypertension and had the most normal body mass index (BMI). Additionally, Cluster 2 had less nocturnal hypoxia as compared to Cluster 3. Cluster 3 (n=68, 29.3%) was the youngest in age, predominantly male, with the highest BMI, cumulative risk score, and prevalence of dyslipidemia of the three clusters.

**Conclusion:** Post-stroke OSA can be categorized into three clinical phenotypes. Patients in Clusters 1 and 3 both had elevated cardiovascular risk and treatment can be based on their distinct characteristics. Patients in Cluster 2 had relatively lower risk of cardiovascular events and the benefits of OSA treatment requires further study.

**Keywords:** obstructive sleep apnea, ischemic stroke, cluster analysis, latent class analysis

## Introduction

Severe obstructive sleep apnea (OSA) doubles the risk of incident stroke and is a risk factor for stroke recurrence and mortality, but can be improved by continuous positive airway pressure treatment.<sup>1</sup> OSA is highly prevalent in stroke patients but compliance with standard continuous positive airway pressure treatment is poor. Consequently, the effectiveness of continuous positive airway pressure treatment for reducing stroke risk is equivocal.<sup>1</sup>

Previous cluster analysis identified three distinct clusters: a “disturbed sleep group,” a “minimally symptomatic group,” and an “excessive daytime sleepiness (EDS) group,” using the Icelandic Sleep Apnea Cohort based on latent class

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analysis (LCA) using clinical symptoms and comorbidities.<sup>2</sup> Keenan et al confirmed and extended these results by recruiting international participants from the Sleep Apnea Global Interdisciplinary Consortium.<sup>3</sup> However, both these analyses were mainly performed on middle-aged patients with obesity. A study by Mazzotti et al using the Sleep Heart Health Study (SHHS) cohort with mean age of  $66.0 \pm 10.5$  y/o and body mass index (BMI) of  $30.4 \pm 5.7$  kg/m<sup>2</sup>, identified four clusters, including the three previously mentioned clusters plus a moderate sleepy subtype; the excessively sleepy subtype had the highest apnea-hypopnea index and increased prevalence and incidence of cardiovascular events compared to the three other clusters.<sup>4</sup> Therefore, phenotypes found by cluster analysis may have prognostic value and characteristics suitable for precision medicine. However, the typical clinical manifestations of OSA, such as daytime sleepiness, are not obvious in stroke patients.<sup>5</sup> Moreover, more than 50% of ischemic stroke patients reported insomnia<sup>6</sup> which could result from depression, anxiety, brain damage, sleep-disordered breathing, medications, and environmental disturbances (eg, in a rehabilitation ward).<sup>7</sup> Therefore, it is questionable whether previously mentioned symptom-based subtypes of OSA can be applied to patients with ischemic stroke. Schutz et al conducted cluster analysis of ischemic stroke patients with OSA diagnosed by home sleep apnea testing based on symptoms, comorbidities and OSA severity index and identified three clusters that differed by age, stroke severity and OSA severity.<sup>8</sup> However, the major determinants found in their study, age, stroke severity and OSA severity, are well-known risk factors for further cardiovascular events and thus fail to provide additional useful information for the management of OSA in ischemic stroke patients.

This study was designed to identify subgroups of moderate-to-severe OSA patients with comorbid ischemic stroke using LCA based on symptoms and comorbidities instead of OSA severity, in order to improve the management of OSA in stroke patients. The study also examined whether patient subgroups differed in demographic, polysomnographic and vascular characteristics.

## Methods

### Participants

This study enrolled consecutive post-acute ischemic stroke patients with OSA who were admitted for rehabilitation at

a teaching hospital. The exclusion criteria were as follows: severely impaired consciousness; unstable medical or neurological status such as active infection or recent transient ischemic attack; previous history of intracranial hemorrhage or malignancy; and chronic kidney disease at stage 3 or higher. Participants with other sleep disordered breathing, such as central sleep apnea syndrome or central hypoventilation, were also excluded.

The study was conducted in accordance with the Declaration of Helsinki. The institutional review board of Chang Gung Medical Foundation approved the study protocol (IRB number: 201802080B0). Informed consent was given by participants and/or their legal guardians if participants had certain degree of cognitive or communicative impairments due to stroke.

### Clinical Evaluation

The researchers collected demographic data and a thorough history of stroke risk factors. We considered smoking (active smokers vs nonsmokers; ex-smokers were considered nonsmokers if they had stopped smoking more than three months prior to stroke onset), hypertension (HTN, history of HTN, or systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg before or two weeks after stroke onset), and diabetes mellitus (history of diabetes mellitus or fasting blood glucose > 126mg/dL). Dyslipidemia was defined based on current lipid levels or taking anti-dyslipidemia medications in the past two weeks. The cut-off values were 240 mg/dL, 160 mg/dL, 40 mg/dL and 200 mg/dL for higher total cholesterol, higher low-density lipoprotein, lower high-density lipoprotein, and higher triglycerides, respectively.<sup>9</sup> A speech-language pathologist confirmed the diagnosis of dysphagia. Cardiac arrhythmia was assessed by 12-lead electrocardiogram or 24-hour Holter electrocardiogram if stroke etiology was uncertain after the initial evaluation. Neck circumference, BMI, Epworth Sleepiness Scale<sup>10</sup> and the Barthel Index (BI)<sup>11</sup> were measured on the same day as polysomnography examination. We used the BI to evaluate activities of daily living and functional outcomes and to represent stroke severity. The EDS is associated with increased incident cardiovascular morbidity and mortality<sup>12,13</sup> and was defined as an Epworth Sleepiness Scale  $\geq 10$ .<sup>10</sup> We categorized underweight as BMI <18.5 kg/m<sup>2</sup>, overweight as BMI  $\geq 24.0$  to <27.0 kg/m<sup>2</sup>, and obesity as BMI  $\geq 27.0$  kg/m<sup>2</sup> according to the definitions of the Health Promotion Administration

of Taiwan. Depression was assessed with the Patient Health Questionnaire-9<sup>14</sup> and defined by a Patient Health Questionnaire-9 score  $\geq 10$ , with a sensitivity of 0.80 (95% CI, 0.62–0.98) and a specificity of 0.78 (95% CI, 0.69–0.83).<sup>15</sup> The cumulative risk score was defined as the sum of the presence of major cardiovascular risk factors, including smoking, obesity, HTN, diabetes mellitus and dyslipidemia.<sup>16</sup>

## Polysomnography

The polysomnography was conducted at the sleep center using a Compumedics Profusion system (Australia). At least six hours of recorded time was required to obtain a valid measurement. We used the American Academy of Sleep Medicine (AASM) scoring manual version 2.0.3 to diagnose sleep apnea<sup>17</sup> and calculated the oxyhemoglobin desaturation index, defined as the average number of desaturation episodes per hour. Apnea was defined as the discontinuation of airflow for  $\geq 10$  seconds; hypopnea was defined as a reduction of  $>30\%$  in airflow for  $> 10$  seconds with either oxygen desaturation  $\geq 3\%$  or an arousal. Diagnosis of OSA was made when  $> 50\%$  of respiratory events were of obstructive or of mixed types. Central sleep apnea syndrome was diagnosed when  $\geq 50\%$  of respiratory events were of central type. We defined moderate-to-severe OSA as  $> 15$  apneas and/or hypopneas per sleep hour (apnea-hypopnea index  $> 15$  events $\cdot h^{-1}$ ).

## Arterial Stiffness

Detailed methods to evaluate arterial stiffness by pulse-wave analysis using the SphygmoCor<sup>®</sup> CPV System (AtCor Medical, Sydney, Australia) have been described elsewhere<sup>18,19</sup> and in our previous work.<sup>20</sup> Briefly, measurements were taken immediately after the patients woke up and before breakfast. For pulse wave calibration, blood pressure was recorded five minutes before vascular measurements over the non-paretic arm. The applanation probe was placed on the radial artery of the non-paretic arm. The ascending aortic waveform was generated from the radial signal using SphygmoCor<sup>®</sup> software (version 9.0)<sup>21</sup> and the augmentation index (AIx) as a measure of systemic arterial stiffness<sup>22</sup> was computed as the difference between the second and first systolic peaks divided by the central pulse pressure. Given that the AIx is associated with heart rate, we used an index corrected for a heart rate of 75 bpm (AIx@75).<sup>23</sup>

## Statistics

Cluster analysis among ischemic stroke patients with previously untreated moderate-to-severe OSA was performed using LCA with 13 clinically relevant variables, including sex, old age (age  $\geq 65$  vs  $< 65$ ), cigarette smoking, EDS (Epworth Sleepiness Scale  $\geq 10$  vs  $< 10$ ), depression (Patient Health Questionnaire-9 score  $\geq 10$  vs  $< 10$ ), obesity (BMI  $\geq 27$ , 24–27, 18.5–24,  $< 18.5$  kg/m<sup>2</sup>), sleep disturbance with sedative use, including hypnotics and sedative antidepressants, comorbidities including atrial fibrillation (Af), diabetes mellitus, dyslipidemia, HTN, recurrent stroke and dysphagia. Models with between two and six clusters were compared and the optimal number of clusters was determined based on meaningful clinical interpretability and parsimony according to the Bayesian information classification indices, a nonsignificant  $\chi^2$  statistic with  $P > 0.05$  (using the bootstrap  $L^2$  value), as well as the bootstrap likelihood ratio test to statistically test the different cluster models. Lower Bayesian information classification values represent better model fit. Once the optimal clustering solution was determined, the LCA calculated the probability of participants being part of each constructed class and assigned each participant membership to the class considering the highest probability. Then we summarized and compared clinical symptoms, demographic characteristics, parameters of OSA and arterial stiffness across classes using the following methods: 1. For continuous and normally distributed variables: analysis of variance followed by post hoc Scheffe's analyses for homogeneous variances or the Welch test followed by post hoc Games-Howell analyses for heterogeneous variances; 2. For continuous and non-normally distributed variables: Kruskal–Wallis one-way analysis of variance followed by post hoc Dunn's multiple-comparison test; 3.  $\chi^2$  or Fisher's exact tests for categorical variables. When group differences were observed with  $\chi^2$  or Fisher's exact tests ( $P < 0.05$ ), we performed between-class comparisons to understand which between-class differences were driving overall associations. Given three pairwise comparisons, a Bonferroni-corrected value of  $P < 0.0167$  was considered a statistically significant between-class difference. Latent Gold 5.0 (Vermunt & Magidson, 2005) and SPSS (IBM SPSS Statistics 25, SPSS Inc., Chicago, IL) were used.

## Results

The study included 232 ischemic stroke patients with moderate-to-severe OSA. On average, the median age was 63.7 years (interquartile range (IQR) 56.7–73.5 years), 69.8% were male, median BMI was 24.3 kg/m<sup>2</sup> (IQR 21.8–26.7 kg/m<sup>2</sup>) and the median BI was 40 (IQR 25–50) due to ischemic stroke. The median duration between stroke onset and polysomnography study was 2.7 months (IQR 1.2–4.8 months). The sample characteristics are summarized in Table 1. Table 2 shows the initial LCA results of two- to six-cluster models. Examining these statistics, the two-cluster model seemed the best fit as it had the lowest Bayesian

information classification value. Five-cluster and six-cluster models had bootstrap  $P < 0.05$ . The results from the bootstrap likelihood ratio test indicated that the three-cluster model was better than the two-cluster model ( $-2LL \text{ Diff} = 41.84$ ,  $P = 0.032$ ). Thus, we selected the three-cluster model as the most appropriate model. The characteristics of the three clusters are described below and summarized in Table 1. The markers of OSA severity, including apnea-hypopnea index and oxyhemoglobin desaturation index, did not differ significantly among the three clusters. Also, the three clusters did not differ significantly in the frequency of sedative usage and the prevalence of EDS.

**Table 1** Demographic, Clinical Characteristics, OSA and Arterial Stiffness Parameters of the Total Cohort and by Clusters

	Overall Cohort	Cluster 1	Cluster 2	Cluster 3	$p^*$
N (%)	232 (100%)	84 (36.2%)	80 (34.5%)	68 (29.3%)	
Clinical variables					
Age (y/o)	63.7 (56.7–73.5)	70.3 (60.4–74.7) <sup>‡</sup>	70.5 (59.7–76.4) <sup>§</sup>	57.8 (52.2–62.2) <sup>‡, §</sup>	< 0.001
Male (n)	162 (69.8%)	18 (21.4%) <sup>†, ‡</sup>	77 (96.2%) <sup>†</sup>	67 (98.5%) <sup>‡</sup>	< 0.001
BMI (kg/m <sup>2</sup> )	24.4 ± 4.1	24.4 ± 5.3 <sup>†, ‡</sup>	22.8 ± 2.6 <sup>†, §</sup>	26.2 ± 2.9 <sup>‡, §</sup>	< 0.001
Smoking (n)	89 (38.4%)	0 <sup>†, ‡</sup>	42 (52.5%) <sup>†</sup>	47 (69.1%) <sup>‡</sup>	< 0.001
EDS (n)	118 (50.9%)	44 (52.4%)	38 (47.5%)	36 (52.9%)	0.757
Depression (n)	93 (40.1%)	27 (32.1%) <sup>†</sup>	45 (56.2%) <sup>†, §</sup>	21 (30.9%) <sup>§</sup>	0.001
Af (n)	44 (19.0%)	27 (32.1%) <sup>†, ‡</sup>	8 (10.0%) <sup>†</sup>	9 (13.2%) <sup>‡</sup>	0.001
DM (n)	98 (42.2%)	40 (47.6%)	26 (32.5%)	32 (47.1%)	0.093
Dyslipidemia (n)	178 (76.7%)	62 (73.8%) <sup>‡</sup>	48 (60.0%) <sup>§</sup>	68 (100.0%) <sup>§, ‡</sup>	< 0.001
Hypertension (n)	202 (87.1%)	80 (95.2%) <sup>†</sup>	55 (68.8%) <sup>†, §</sup>	67 (98.5%) <sup>§</sup>	< 0.001
Recurrent stroke (n)	70 (30.2%)	29 (34.5%)	16 (20.0%)	25 (36.8%)	0.048
Dysphagia (n)	53 (22.8%)	24 (28.6%) <sup>‡</sup>	29 (36.2%) <sup>§</sup>	0 <sup>‡, §</sup>	< 0.001
Barthel index	40.0 (25.0–50.0)	30.0 (21.3–45.0) <sup>‡</sup>	32.5 (20.0–48.8) <sup>§</sup>	45.0 (40.0–53.8) <sup>‡, §</sup>	< 0.001
Neck circumference (cm)	38.0 (35.5–40.0)	35.0 (33.1–38.0) <sup>†, ‡</sup>	38.0 (37.0–39.0) <sup>†, §</sup>	40.0 (38.6–42.0) <sup>†, §</sup>	< 0.001
Cumulative risk score	3.0 (2.0–3.0)	2.5 (2.0–3.0) <sup>‡</sup>	2.0 (1.0–3.0) <sup>§</sup>	4.0 (3.0–4.0) <sup>‡, §</sup>	< 0.001
Sedatives usage (n)	98 (42.2%)	36 (42.9%)	32 (40.0%)	30 (44.1%)	0.871
OSA parameters					
AHI (events/hour)	40.5 (27.7–56.6)	44.9 (27.6–55.4)	37.8 (25.5–55.3)	42.5 (30.4–58.2)	0.428
ODI (events/hour)	34.4 (20.3–55.6)	40.1 (20.8–56.1)	28.1 (19.6–57.6)	35.9 (19.7–54.4)	0.649
Apnea index (events/hour)	15.5 (6.5–40.5)	14.6 (5.1–33.7)	14.6 (7.7–44.1)	17.3 (6.3–43.2)	0.240
OA index (events/hour)	10.0 (4.5–20.4)	9.5 (2.9–18.3)	9.7 (5.4–18.7)	13.1 (4.8–28.2)	0.232
CA index (events/hour)	0.4 (0–1.9)	0.3 (0–1.5)	0.8 (0–2.4)	0.5 (0–1.3)	0.094
MA index (events/hour)	1.2 (0–7.2)	1.0 (0–8.8)	1.0 (0–7.3)	1.4 (0–6.4)	0.874
Hypopnea index (events/hour)	19.3 (12.2–26.0)	22.7 (14.6–31.0) <sup>†, ‡</sup>	15.2 (9.1–23.9) <sup>†</sup>	19.2 (12.5–23.0) <sup>‡</sup>	0.001
Mean SpO <sub>2</sub> (%)	93.0 (91.6–94.6)	93.0 (91.4–94.0)	93.0 (91.7–94.7)	93.8 (92.4–95.0)	0.054
Minimum SpO <sub>2</sub> (%)	77.0 (65.0–82.8)	76.0 (66.0–82.0)	79.0 (69.3–83.0) <sup>§</sup>	75.0 (57.0–81.0) <sup>§</sup>	0.039
Sleep efficiency (%)	71.3 (60.0–80.9)	71.4 (57.0–80.9)	68.5 (56.2–76.7) <sup>§</sup>	74.6 (65.2–86.1) <sup>§</sup>	0.007
Alx@75 (%)	27.8 ± 8.8	30.4 ± 9.0 <sup>†</sup>	26.0 ± 9.4 <sup>†</sup>	27.0 ± 6.9	0.007

**Notes:** Values are means ± standard deviation or medians (interquartile ranges) unless otherwise stated. \*P value from analysis of variance and chi-square or Fisher exact tests across 3 clusters. <sup>†</sup>Cluster 1 vs 2 comparisons significant. <sup>‡</sup>Cluster 1 vs 3 comparisons significant. <sup>§</sup>Cluster 2 vs 3 comparisons significant.

**Abbreviations:** BMI, body mass index; EDS, excessive daytime sleepiness; Af, atrial fibrillation; DM, diabetic mellitus; AHI, apnea-hypopnea index; ODI, oxyhemoglobin desaturation index; OSA, obstructive sleep apnea; OA, obstructive apnea; CA, central apnea; MA, mixed apnea; SpO<sub>2</sub>, oxyhemoglobin saturation by pulse oximetry; Alx@75, augmentation index adjusted for heart rate at 75 beats per minute.

**Table 2** Model-Fit Statistics for Latent Class Analysis Results

Number of Clusters	BIC	LL	p value*
2	4130.2121	-1975.235	0.188
3	4180.9677	-1954.315	0.090
4	4230.2667	-1932.668	0.064
5	4295.2216	-1918.848	0.026
6	4363.6787	-1906.779	0.020

**Note:** \* $\chi^2$  statistic using the bootstrap L2 value.

**Abbreviations:** BIC, Bayesian information criteria; LL, log likelihood.

Cluster 1 was older in age, predominantly female (78.6%) and had the highest prevalence of Af and the lowest rate of smoking of the three clusters. Although the severity of OSA did not differ among the three clusters, the hypopnea index was highest in Cluster 1. In addition, patients in Cluster 1 had significantly higher AIX@75 than those in Cluster 2.

Cluster 2 was older in age, predominantly male (96.3%) and had the highest prevalence of depression, the lowest prevalence of HTN, and the most normal BMI. Although the prevalence of recurrent stroke differed significantly among the three clusters ( $P = 0.048$ ), post-hoc analysis only revealed a trend that patients in Cluster 2 had lower prevalence of recurrent stroke than those in Clusters 1 and 3. Additionally, Cluster 2 had a higher level of minimum oxyhemoglobin saturation by pulse oximetry and lower sleep efficiency compared to Cluster 3.

Cluster 3 was predominantly male (98.5%), the youngest in age, and had the highest BMI, BI, neck circumference, prevalence of dyslipidemia, and cumulative risk scores and the lowest prevalence of dysphagia of the three clusters.

## Discussion

The LCA of subacute ischemic stroke patients with moderate-to-severe OSA reveals three distinct clusters based on demographic data and medical comorbidities. Clusters 1 and 2 contained relatively older patients with differing predominant sexes and extent of comorbidities. Male-predominant Cluster 3 contained patients of relatively young age with the highest BMI and prevalence of comorbidities.

Phenotypes found by previous large cohort studies<sup>2-4</sup> are not applicable to ischemic stroke patients with OSA. As the typical clinical manifestations of OSA, such as obesity and daytime sleepiness, are not obvious in post-acute stroke patients,<sup>5,24</sup> the prevalence of EDS did not differ significantly among the three clusters found in this

study. Given the multifactorial etiology of post-stroke insomnia mentioned above, the prevalence of sedative usage also did not differ among the three clusters. Results of this study are consistent with previous studies<sup>8</sup> of ischemic stroke patients with OSA which have suggested that EDS and insomnia are not major determinants in LCA.

Participants in Clusters 1 and 2 were older on average and the main difference between them was sex. The significantly higher prevalence of Af in female-predominant Cluster 1 supports previous studies of ischemic stroke patients that found Af was more prevalent in females.<sup>25</sup> Increased AIX was found to be associated with new-onset Af and prevalence of Af.<sup>26,27</sup> A 10% absolute increase in AIX resulted in an increase in cardiovascular events of 26% and all-cause mortality of 38%.<sup>28</sup> Our finding of a significantly higher AIX@75 and prevalence of Af in Cluster 1 patients as compared to age-matched patients in Cluster 2 is in agreement with these findings and suggests that patients in Cluster 1 may require more aggressive treatment for OSA and comorbidities compared to those in Cluster 2. Park et al found that the hypopnea index was a more important predictor of heart failure and coronary artery disease than the apnea index and that patients with hypopnea-predominant OSA had a significantly larger female to male ratio as compared to those with apnea-predominant OSA.<sup>29</sup> The findings that female-predominant Cluster 1 had the highest hypopnea index of the three clusters and that Af is closely related to coronary artery disease and heart failure<sup>30</sup> further support our inference based on elevated AIX@75 that the risk of cardiovascular events and mortality was higher in Cluster 1 patients compared to those in Cluster 2. Studies have found that non-anatomical pathogenesis of OSA cause dynamic obstruction of the airway and hypopnea, while anatomical pathogenesis of OSA causes static obstruction and apnea.<sup>29</sup> Together with the findings that patients in Cluster 1 had the thinnest neck circumference, Cluster 1 patients may be more likely to have nonanatomic pathogenesis of OSA and are good candidates for alternative therapy along with standard continuous positive airway pressure treatment, as suggested by Eckert et al.<sup>31</sup>

In contrast to Cluster 1, patients in Clusters 2 and 3 were mainly male and the major difference between these two clusters was age. In addition, participants in Cluster 2 had the most normal BMI and lowest prevalence of HTN, and tended to have the lowest cumulative risk score for cardiovascular diseases and recurrent stroke prevalence of



the three clusters, which supports previous findings that the mortality risk of OSA among men with an apnea-hypopnea index  $> 50$  decreased with increasing age.<sup>32</sup> The mechanisms for this perplexing phenomenon are not well understood. With aging, the arousal threshold is reduced, sleep fragmentation is increased, and the level of nocturnal hypoxia is decreased for a given apnea-hypopnea index.<sup>33</sup> Therefore, the elderly with OSA have less nocturnal intermittent hypoxia and its related consequences.<sup>33</sup> Our findings that participants in Cluster 3 had better sleep efficiency and lower levels of minimal oxyhemoglobin saturation by pulse oximetry as compared to participants in Cluster 2 are in agreement with these results. Alternatively, the protective effect against mortality of increasing age might result from the fact that only patients who could successfully adapt to nocturnal respiratory events could survive into older age.<sup>32</sup> Whether treatment for OSA provides clinical benefits for patients in Cluster 2 requires further study. However, Cluster 2 patients had the highest prevalence of depression. Given that post-stroke depression is not consistently associated with age and sex,<sup>34</sup> neurocognitive dysfunction due to OSA might be more severe in patients in Cluster 2, a possibility that merits further study.

Patients in Cluster 3 were the youngest and had the highest BMI, neck circumference, BI, and cumulative risk score of all three clusters. The characteristics of participants in Cluster 3 are similar to typical OSA presentation, including being male, overweight and having a thick neck.<sup>35</sup> Given that AIX increases with age,<sup>36</sup> the non-significant difference in AIX@75 between patients in Cluster 3 and their older counterparts in Clusters 1 and 2 suggests that Cluster 3 has elevated AIX and increased risk of cardiovascular events and mortality.<sup>28</sup> In contrast to Cluster 1, patients in Cluster 3 had the thickest necks and apnea-predominant OSA, and may have primarily anatomic contributors to the pathophysiology of OSA. Therefore, novel alternative therapies for OSA may be ineffective. That Cluster 3 had the highest BI is in agreement with previous observations that age independently and selectively influences stroke outcomes regarding the activities of daily living.<sup>37</sup> That Cluster 3 also had the lowest rate of dysphagia is also consistent with previous findings that old age is an independent predictor of dysphagia, chest infection, or aspiration within the six months after a stroke.<sup>38</sup>

This study has several limitations. Firstly, the study recruited a highly selective group of post-acute ischemic

stroke patients who were admitted for inpatient rehabilitation with moderate-severe OSA. Therefore, our results cannot be extrapolated to ischemic stroke patients with mild OSA and to patients with mild or severe stroke severity who are not suitable for inpatient rehabilitation. However, the clinical impact of mild OSA on stroke recurrence, recovery and mortality seems to be unremarkable. Secondly, sleep disturbance was determined by whether or not patients were prescribed sedatives, rather than by subjective symptoms or objective measures. Given that environmental factors, such as residing in a rehabilitation ward, strongly influence sleep, inpatients commonly report subjective symptoms of sleep disturbance, so we selected severe sleep disturbance with sedative use as our variable in the LCA. Finally, future longitudinal research is suggested to validate the inferences of this cross-sectional analysis.

## Conclusions

Ischemic stroke patients with moderate-to-severe OSA can be categorized into three clusters based on age, sex, and medical comorbidities. The results of LCA have clinical relevance and applicability by providing valuable information for risk stratification and treatment selection for OSA.

## Abbreviations

OSA, obstructive sleep apnea; EDS, excessive daytime sleepiness; LCA, latent class analysis; BMI, body mass index; HTN, hypertension; BI, Barthel index.

## Author Contributions

All authors met the following conditions 1, 2, 3, 4 and 5.

1. 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.
2. Have drafted or written, or substantially revised or critically reviewed the article.
3. Have agreed on the journal to which the article will be submitted.
4. Reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage.
5. Agree to take responsibility and be accountable for the contents of the article.

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## Disclosure

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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