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Incidence of Stroke and Mortality in Chinese Patients with Sleep-Breathing Disorders: A Clinical Population-Based (CPB) Study

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Sleep-breathing disorders are associated with inflammatory, metabolic, and vascular diseases. The objective of this study was to investigate the incidence of stroke and death in patients with sleep-breathing disorders.

Material/Methods: The anthropometric characteristics, demographic data, and incidence of stroke of 1492 Chinese patients with mild, moderate, or severe sleep apnea were collected. The apnea-hypopnea index was used to define sleep-breathing disorders. Imaging modalities were used to validate the diagnosis of stroke. Death during hospitalization or during follow-up was noted. Multivariate analysis was performed for the incidence of stroke and mortality at the 95% of confidence level.

Results: Among enrolled patients, 401 (27%) patients had at least 1 event of stroke. Patients who had at least 1 event of stroke were more likely to be younger ($p<0.0001$), female ($p=0.0013$), and to have comorbidities. Among enrolled patients, 127 died due to stroke or other diseases. Sixteen of the patients who died had no stroke event(s) and 111 patients who died had at least 1 event of stroke. Stroke events ($p=0.023$) and biomedical burden of patients were associated with the death of patients with sleep-breathing disorders.

Conclusions: Age, sex, and the other existing disease(s) of patients with sleep-breathing disorders may be associated with stroke event(s). Also, stroke event(s) and comorbidities may be associated with mortality in this Chinese population.

MeSH Keywords: **Mortality • Polysomnography • Sleep • Sleep Apnea Syndromes • Sleep Apnea, Obstructive • Stroke**

Abbreviations: **STROBE** – Strengthening the Reporting of Observational Studies in Epidemiology

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Background

Sleep-breathing disorders are associated with impaired palate-pharyngeal collapse, poor sleep, repetitive airway obstruction, and decreased muscle tone of the pharyngeal area [1]. Also, sleep-breathing disorders are associated with inflammatory, metabolic, and vascular diseases [2] and affect about 5% of Chinese people [3]. They also cause chronic hypoxia and inflammatory changes in the brain, leading to cerebrovascular disease (e.g., stroke event(s)) [4]. Vasomotor reactivity is altered in patients with stroke. Stroke occurs when blood vessels that carry oxygen and nutrients to the brain are blocked by a clot, burst, or are ruptured.

Unfortunately, sleep-breathing disorders are underdiagnosed in China. Stroke is the leading cause of death in China, causing 20% of all deaths annually [5]. It is important to understand the risk factors of stroke for better management. Hypertension, diabetes mellitus, atrial fibrillation, obesity, and smoking are proven risk factors for stroke [6]. The absolute numbers of stroke victims, the morbidity and mortality rates, and the associated social burden are all high and growing in China. Inadequate changes in persistent risk factors, or the ongoing effects of less-recognized risks, can explain the high burden of stroke [7]. However, there has been little research in China on the association of anthropometric and demographic data of patients with sleep-breathing disorders with the incidence of stroke and mortality.

The aim of this clinical population-based study was to investigate the incidences of stroke and death in Chinese patients with sleep-breathing disorders. We also explored the association between demographic characteristics of patients and stroke event(s).

Material and Methods

Ethics approval and consent to participate

The protocol (YGZ/CL/15/19 dated 12 January 2019) of the study was approved by the Institutional Review Board of the Affiliated Hospital of Yangzhou University. An informed consent form was signed by all patients or their relatives regarding examinations, radiology, treatment, and publication of the study in all formats irrespective of time and language during hospitalization. The study reporting adhered to the law of China, the Declaration of Helsinki (V2008), and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cohort studies statement.

Inclusion criteria

Based on a chart review, we included patients with mild, moderate, or severe sleep apnea (apnea-hypopnea index 5 or more) who were 18 years and older, able to perform daily living activities, able to walking 400 m, able to climb 10 steps without resting, with no reported use of assistive equipment and/or device for mobility, and with no other sleeping problems like restless legs.

Exclusion criteria

We excluded patients who had previous events of stroke and epilepsy, as well as those who were treated with oxygen and had an apnea-hypopnea index of 4 or less (normal sleep apnea).

Data collection

We collected data on the incidence of stroke in the enrolled patients, as well as anthropometric and demographic data collected by interview during follow-up or by telephone calls. Deaths during hospitalization or in follow-up were recorded.

Apnea-hypopnea index assessment

The enrolled patients underwent 6 consecutive nights of in-home polysomnography using an 8-channel Medilog recorder (9000, Oxford, Chicago, IN, USA). The monitoring montage included 2 electroencephalogram channels, bilateral electrooculogram, submental electromyogram, 2 channels of anterior tibialis submental electromyogram, and a nasal-oral thermistor. Polysomnographic all-night recordings were made. The apnea-hypopnea index was defined as the sum of all apneas and hypopneas occurring per hour of sleep (e.g., an apnea-hypopnea index of 5 means 5 apneas and/or hypopneas events/hour) [8]. The perfect or nearly perfect completion of the airflow for a minimum of 10 s was considered as apnea and 30% below perfect completion of the airflow for a minimum of 10 s was considered as hypopnea [9]. Apnea-hypopnea index assessment was validated by physicians with a minimum of 5 years of experience.

Stroke assessment

Magnetic resonance imaging (MRI) and/or computed tomography (CT) were performed if patients had symptoms like temporary weakness in the upper and/or lower extremities, were permanently paralyzed on one side of the body, were unable to speak, or had had face drooping, numbness, gait disturbances, dizziness, blurred vision, severe headache, muscle stiffness, and/or dysphagia. Stroke was confirmed by physicians with a minimum of 5 years of experience using imaging modalities. Patients who had transient weakness but without imaging evidence of loss of circulation were not confirmed as having had a stroke attack.

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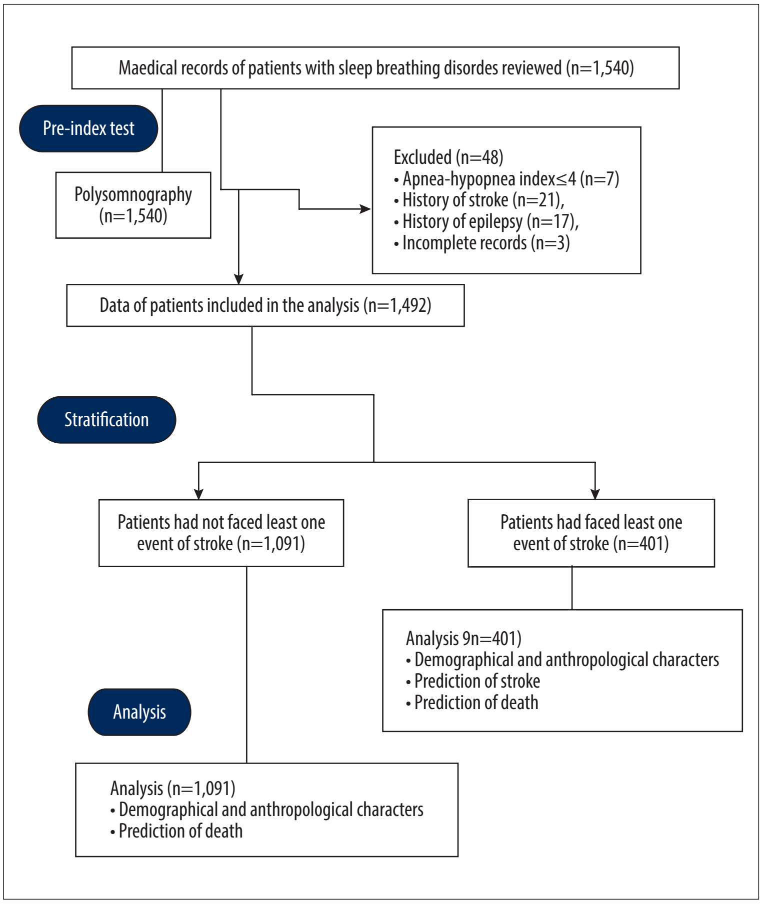

Figure 1. Flowchart of the study.

Statistical analysis

SPSS Statistics, 25.0, IBM Corporation, New York, USA was used for statistical analysis. Logistical regression analysis was performed for the anthropometric and demographic characteristics to predict stroke and mortality. Fisher's exact test for constant variables and Mann-Whitney *U* test for continuous variables were used for statistical analysis. All results were considered significant at 95% confidence level.

Results

Enrollment

From 1 January 2014 to 10 April 2018, medical records (with follow-up data) of 1450 patients with sleep-breathing disorders available at the Affiliated Hospital of Yangzhou University, China during a routine check-up were reviewed. Among them, 7 patients had apnea-hypopnea index ≤4 (≤4 apneas and/or hypopneas events/hour), 21 patients had known history of stroke, 17 patients had known history of epilepsy, and complete records of 3 patients were not available; therefore, these patients were excluded from the study (Figure 1).

Demographical and anthropological characteristics

Medical records including 2 years of follow-up of 1492 patients with ≥5 apnea-hypopnea index (≥5 apneas and/or hypopneas events/hour) were included in the analysis. Among them, 401 patients had at least 1 event of stroke and were subjected to intravenous injection of tissue plasminogen activator within 5 h after symptoms began. Patients who had at least 1 event of stroke tended to be younger than patients who had not had a stroke event(s) (p<0.0001), were more likely to be female (p=0.0013), and were more likely to have comorbidities (e.g., hypertension, diabetes, atrial fibrillation, obesity, apnea-hypopnea index, coronary artery disease, hyperlipidemia, congestive heart failure, and atrial fibrillation). Also, Han Chinese race patients had higher frequencies of stroke event(s) (p<0.0001). The other demographical and anthropological characters of the enrolled patients are presented in Table 1.

Incidence of stroke

All demographical and anthropological characteristics were subjected to multivariate analysis for finding factors associated with the stroke event(s). Stroke events were more likely to have occurred in younger (p=0.012) and female (p=0.032)

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Table 1. The demographic, anthropological, and comorbidity variables of the enrolled patients.

Characters		Population			Comparison between patients with at least one event of a stroke and patients without stroke event(s)
		Total	Cohort: Patients with at least one event of a stroke	Cohort: Patients without stroke event(s)	
Records of patients included in the analysis		1,492	401	1,091	*p*-Value
Age	Minimum	18	20	18	<0.0001
	Maximum	69	65	69	
	Mean±SD	58.12±6.53	55.52±4.45	61.45±6.48	
Gender	Male	502 (34)	109 (27)	393 (36)	0.0013
	Female	990 (66)	292 (73)	698 (64)	
Hypertension		412 (28)	225 (56)	187 (17)	<0.0001
Diabetes mellitus (random blood glucose >140 mg/dL)		389 (26)	189 (47)	200 (18)	<0.0001
Atrial fibrillation		312 (21)	192 (48)	120 (11)	<0.0001
Obesity (body mass index ≥25 kg/m^2)		312 (21)	188 (47)	124 (11)	<0.0001
Smoking (current+previous)		429 (29)	201 (50)	228 (21)	<0.0001
Alcoholic (current+previous)		82 (6)	21 (5)*	61 (6)	0.898
Apnea-hypopnea index score (events/hour)		12.45±3.45	13.52±4.41	11.11±3.12	<0.0001
Forced expiratory volume in one second (L)		2.75±0.81	2.85±0.83	2.65±0.77	<0.0001
Neck circumference (cm)		35.91±3.89	36.01±3.95*	35.82±3.61	0.38
Waist circumference (cm)		84.71±7.21	85.22±7.89	84.01±6.88	0.004
Hip circumference (cm)		95.22±7.58	96.28±6.51	94.94±7.22	0.001
Minimum peripheral capillary oxygen saturation**		86.42±4.45	84.81±3.89	88.12±5.12	<0.0001
Coronary artery disease		152 (10)	55 (14)	97 (9)	0.012
Hyperlipidemia		232 (15)	102 (25)	130 (12)	<0.0001
Congestive heart failure		107 (7)	45 (11)	62 (6)	0.0004
Atrial fibrillation		109 (7)	42 (10)	67 (6)	0.007
Ethnicity	Han Chinese	1,259 (84)	370 (92)	889 (81)	<0.0001
	Mongolian	180 (12)	28 (7)	152 (14)	
	Tibetan	53 (4)	3 (1)	50 (5)	
Epworth sleepiness score		6.71±2.31	6.67±2.35*	6.91±2.18	0.065

Constant data are represented as number (percentage) and continuous data are presented as mean±SD. Fisher's exact test for constant variables and Mann-Whitney *U*-test continuous variables were used for statistical analysis. A $p<0.05$ was considered significant. * Insignificant difference with reference to those who had not faced stroke; ** Average of more than 1-min reading.

patients. Comorbidities (e.g., hypertension, diabetes, atrial fibrillation, obesity, apnea-hypopnea index, coronary artery disease, hyperlipidemia, congestive heart failure, and atrial fibrillation) and smoking (p=0.035) were associated with event(s) of stroke (Table 2).

Incidence of mortality

Among enrolled patients, 127 patients died due to stroke or other disease(s). Sixteen of the patients who died had not had a stroke event(s) and 111 dead patients had faced at least one event of a stroke (Figure 2). All demographical and

Table 2. Multivariate analysis for finding factors associated with stroke event(s).

Characters	*p*-Value	95% CI	OR
Records of patients included in the analysis	401		
Age*	0.012	2.3–3.3	2.1
Gender*	0.032	2.5–3.1	1.8
Hypertension*	0.021	2.6–3.0	1.7
Diabetes mellitus* (random blood glucose >140 mg/dL)	0.025	2.65–3.05	1.65
Atrial fibrillation*	0.026	2.6–3.0	1.68
Obesity* (body mass index ≥25 kg/m^2)	0.031	2.7–3.1	1.64
Smoking* (current+previous)	0.035	2.75–3.15	1.66
Apnea-hypopnea index score* (events/hour)	0.036	2.7–3.1	1.67
Forced expiratory volume in one second (L)	0.052	2.1–3.2	1.1
Neck circumference (cm)	0.091	2.0–3.2	1.2
Minimum peripheral capillary oxygen saturation	0.093	2.1–3.4	1.3
Coronary artery disease*	0.032	2.75–3.15	1.65
Hyperlipidemia*	0.035	2.8–3.2	1.69
Congestive heart failure*	0.041	2.65–3.15	1.65
Atrial fibrillation*	0.042	2.6–3.05	1.64
Ethnicity	0.093	2.1–3.3	1.2
Alcoholic (current+previous)	0.06	2.2–2.9	1.3
Epworth sleepiness score	0.053	2.3–3.1	1.35
Waist circumference	0.089	2.2–3.2	1.4
Hip circumference	0.087	2.12–3.3	1.35

A $p<0.05$ was considered significant. * Significant parameter associated with stroke event(s). Data of patients who had not faced stroke event(s) were considered as the reference standard.CI – confidence interval; OR – odd ratio.

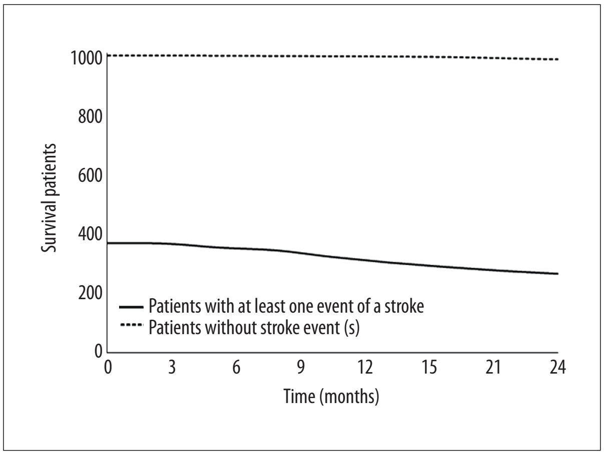

Figure 2. Survival analysis curve.

anthropological characters were subjected to multivariate analysis for finding factors associated with death. Hypertension (p=0.029), diabetes (p=0.027), atrial fibrillation (p=0.028), coronary artery disease (p=0.042), hyperlipidemia (p=0.044), congestive heart failure (p=0.046), atrial fibrillation (p=0.044), and stroke event(s) (p=0.023) were associated with mortality (Table 3).

Discussion

In this cohort of Chinese patients with sleep-breathing disorders, compared to patients without stroke, patients with stroke tended to be younger and female, and to have comorbidities, including hypertension, diabetes, obese, and cardiac disease(s). This study shows that age, sex, and other existing disease(s) are predictors of stroke, whereas stroke event(s) and comorbidities are the predictors of mortality. The results of the study were consistent with prospective cohort studies [8,10]. Sleep-breathing disorders may suggest the causative clues for stroke and mortality in Chinese populations.

The most significant finding in the study was the unusual association between young females and stroke event(s), which

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Table 3. Multivariate analysis for finding factors associated with mortality.

Characters	*p*-Value	95% CI	OR
Records of patients included in the analysis	127		
Age	0.062	2.35–3.51	1.25
Gender	0.082	2.4–3.4	1.26
Hypertension*	0.029	2.6–3.2	1.8
Diabetes mellitus* (random blood glucose >140 mg/dL)	0.027	2.55–3.25	1.81
Atrial fibrillation*	0.028	2.6–3.3	1.82
Obesity (body mass index ≥25 kg/m^2)	0.061	2.45–3.25	1.27
Smoking (current+previous)	0.055	2.6–3.1	1.5
Apnea-hypopnea index score (events/hour)	0.066	2.65–3.45	1.45
Forced expiratory volume in one second (L)	0.082	2.45–3.25	1.5
Neck circumference (cm)	0.521	2.35–3.35	1.59
Minimum peripheral capillary oxygen saturation	0.123	2.1–3.1	1.1
Coronary artery disease*	0.042	2.45–3.05	1.75
Hyperlipidemia*	0.044	2.65–3.1	1.69
Congestive heart failure*	0.046	2.7–3.2	1.75
Atrial fibrillation*	0.044	2.65–3.15	1.81
Ethnicity	0.123	2.15–3.3	1.2
Stroke event(s)*	0.023	2.75–3.05	1.87
Alcoholic (current+previous)	0.069	2.65–3.45	1.25
Epworth sleepiness score	0.058	2.45–3.4	1.31
Waist circumference	0.122	2.1–3.1	1.35
Hip circumference	0.132	2.2–3.2	1.32

A $p<0.05$ was considered significant. * Significant parameter associated with mortality. Data of patients who had survived were considered as the reference standard. CI – confidence interval; OR – odd ratio.

has not been shown clearly in any other studies of Chinese patients with sleep-breathing disorders. The results of our study are consistent with retrospective cohort studies in Taiwan [6] and Korea [10], a community-based study in Australia [11], and prospective studies in America [9,12]. Hormonal and structural differences in young women with sleep-breathing disorders may contribute to vascular inflammation and oxidative stress, which can increase the risk for stroke [13]. Also, women have less upper airway capacity compared to men when seated [6]. In addition, inflammation in women tends to be higher than in men [13]. Further research is required to explain the incidence of stroke events in younger Chinese women who have sleep-breathing disorders.

Our study found that only comorbidities and stroke event(s) were significant predictors of death. The results of the study were consistent with a sleep study [14], a community-based study [11], and a prospective cohort study [8]. Prolonged blood oxygen desaturation and short sleep duration with medical bioburden are major causes of mortality [15]. Early prevention and attention should be paid to sleep-breathing disorders to reduce stroke events and mortality.

Waist, neck, and hip circumferences and ethnicity were not associated with stroke event(s) and mortality. Results of the study were in line with a Chinese population-based, cross-sectional study [16]. Large waist and neck circumferences can contribute to sleep-breathing disorders [2,3] but not to the event(s) of stroke and mortality. Ethnicity may influence craniofacial phenotyping and severity of sleep-breathing disorders [17], but may not influence event(s) of stroke and mortality. Waist, neck, and hip circumferences and ethnicity do not add much incremental information when sex, age, and comorbidities are known.

There are several limitations to our study; such as the low specificity of stroke symptoms, the issue of generalizability to the rest of world because Chinese people have craniofacial skeletal restriction and are slimmer than African people, while white people are more likely to have bony and soft

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tissue abnormalities [17]. Respiratory movement, the length of sleep, and the stage of sleep were not evaluated. Only 27% of patients had at least 1 event of stroke, which was higher than in a retrospective cohort study [10] but lower than in a prospective study [12]. Central apnea, respiratory, and muscle weakness aspiration may be associated with the event(s) of stroke [9,10] but the study did not use these parameters for in-depth analysis. Stroke studies generally show that older age is associated with stroke in both men and women, but the present study reported that stroke events occurred more in younger women. The pre- and post-menopausal characteristics of women can substantially modify the results and background pathology [2].

Conclusions

Chinese younger females with sleep-breathing disorders had a high incidence of an event(s) of stroke. Age, sex, and the other existing disease(s) of Chinese patients with sleep-breathing disorders may be associated with stroke event(s). Also, stroke events and comorbidities may have an association with mortality. A longer period of follow-up or a longitudinal study is required to predict the other independent factors for stroke and death. Clinicians should also regularly inquire about sleep when creating a comprehensive care plan for patients during routine screening. Also, maximum creative and economic factors need to be developed to identify patients who are at risk so they can receive additional screening and management.

Acknowledgments

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Availability of data and materials

The datasets used and analyzed in this study are available from the corresponding author on reasonable request.

Conflict of interest

None.

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