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Sleep disorders and airway diseases

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Sleep disorders and airway diseases

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Editorial: Sleep disorders and airway diseases

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Editorial on the Research Topic
Sleep disorders and airway diseases

Various medical disease states frequently exhibit sleep disorders, which have negative effects on patients' quality of life. Due to their detrimental effects on patients' neuropsychology and medical conditions, sleep disorders cause patients' comorbidities to become more severe and uncontrollable. Therefore, it is crucial to take a strategic approach to the diagnosis and treatment of sleep disorders in medical pathologies. Sleep disorders and airway diseases are closely related among these medical pathologies. Asthma and chronic obstructive pulmonary disease (COPD), as well as COVID-19 and post-COVID-19 diseases, can affect sleep architecture, lower the quality of sleep, and cause refractory insomnia or symptomatic obstructive sleep apnea (OSA). These reciprocal effects negatively impact the neuropsychological status, quality of life, and overall health of patients. Thus, the Research Topic "*Sleep disorders and airway diseases*" achieves great success with 15 published articles that cover all the aspects of sleep, from airway disease interactions in age-related populations and comorbidities to diagnosis and treatment approaches based on the use of technology and artificial intelligence (AI).

Firstly, OSA is the typical disease entity that manifests as a result of the interaction between sleep disorders and the upper airway at night. In children with adenotonsillar hypertrophy, the prevalence of OSA is high due to the occlusion of the upper airway. The use of respiratory polygraphy is more comfortable for children and is used to confirm the diagnosis of OSA. In this Research Topic, Tran-Minh et al. demonstrated a significant correlation between the apnea-hypopnea index (AHI) and the severity level of tonsillar and adenoid hypertrophy in children with snoring. Interestingly, treatment with antileukotriene receptors (ALRs) for non-severe hypertrophy or surgical therapy for those with severe hypertrophy could significantly reduce the mean AHI in this population with OSA. In fact, ALRs could be considered a first-line anti-inflammatory treatment for children with OSA and asthma. In addition, the cohort study conducted by Duong-Quy et al. consisting of 139 asthmatic

children aged more than 5 years with comorbid OSA also showed that the severity of asthma and the symptoms related to OSA in these children significantly improved after 3-month-long and 6-month-long treatment with LRA combined with standard therapy for asthma. Moreover, asthma and OSA are the most common chronic respiratory disorders in children within bidirectional correlation. If left untreated, OSA may cause attention deficit hyperactivity disorder (ADHD) symptoms in asthmatic children. Therefore, prompt diagnosis of OSA will lead to an accurate control strategy in patients with asthma (Nguyen-Ngoc-Quynh et al.).

Recently, the overlap between obstructive lung disease (OLD) and OSA (OLDOSA) has been identified as a common phenotype of subjects with OSA. Therefore, personalized approaches to the diagnosis and treatment of subjects with OLDOSA are necessary in clinical practice. Besides OSA, the sleep quality of patients with asthma and COPD should be considered a crucial outcome in the management of these patients. The results of a cross-sectional study consisting of 390 patients with asthma and COPD conducted by Aldabayan and published in this Research Topic revealed that these patients had significantly reduced sleep quality, anxiety, and depression. The association between sleep duration, respiratory symptoms, asthma, and COPD in adults has been also well-demonstrated by Ruan et al.. The results of this study suggested that both long and short sleep duration might be associated with cough and dyspnea and that short sleep duration may be an independent risk factor for wheezing, asthma, and COPD. This relevant information might provide new insights into the management of respiratory symptoms and sleep quality.

Secondly, many subjects with acute respiratory symptoms due to COVID-19 suffer from post-COVID-19 sleep disorders. An online survey of the post COVID-19 conditions in various countries showed that nearly 80% of subjects had sleep disorders, including insomnia, sleep-disordered breathing, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders (Tedjasukmana et al.). Thus, sleep disorders are the major problem in post-COVID-19 conditions and may affect patients' quality of life (QoL), making the existence of sleep disturbances a concern in the period post-COVID-19 (Tedjasukmana et al.). Furthermore, sleep disorders may also be seen in acute or chronic non-infectious diseases such as after a stroke or in the case of Down syndrome. This Research Topic also includes the results of the study on the relationship between sleep disorders and the prognosis of neurological function after stroke (Zhang et al.). In fact, low sleep quality and unusual nocturnal total sleep time (long or short) may be associated with short-term poor neurological function after stroke, and a high risk of OSA may be associated with a higher risk of all-cause death after stroke (Zhang et al.). A recent descriptive cross-sectional study conducted by Hoang-Anh et al. which was published in this Research Topic suggests that OSA may be a prognostic factor of cerebral infarction as well as cardiovascular diseases such as hypertension. Moreover, poor sleep quality is recognized as a major risk factor for poor health, increasing the incidence of serious chronic diseases. Additionally, the prevalence of OSA is significantly greater in patients with Down syndrome compared to the general population as a result of genetic, anatomical, endocrine, and metabolic abnormalities (Nguyen et al.). The consequences of sleep disruption due to OSA are very serious, especially in terms of neurocognitive and cardiovascular effects, leading to reduced life expectancy and quality of life in this population.

Thirdly, sleep medicine has reaped the benefits that have come with the progress of modern technology in terms of diagnosis and treatment by using machine learning, wearable devices, smartphone applications, and telemedicine. The primary results in this field have contributed to one-third of published manuscripts in this Research Topic. Liu et al. showed the effectiveness of using a machine learning approach for differentiating OSA patients with and without mild cognitive impairment and providing potential neuroimaging evidence for cognitive impairment caused by OSA. Particularly, during the COVID-19 pandemic, due to a shortage of medical staff and equipment, diagnosing sleep disorders and OSA became more difficult than ever before (Tran et al.). The state-of-the-art review published on this Research Topic suggests that the digital transformation of healthcare might provide the advantage of cutting-edge technologies and innovations that deliver sustainable service and medical solutions to patients, medical staff, and healthcare bodies (Tran et al.). The authors of this review also suggest that home sleep apnea tests could be a promising alternative sleep study solution for patients with OSA because it may help to save time and money while enabling improved interaction between physicians and patients. Polysomnography (PSG), which is manually scored by a sleep technologist, is currently the gold standard for diagnosis of OSA severity. However, PSG scoring takes time and effort and has a lot of inter-rater variability. Hence, PSG autoscoring can be done by using a deep learning-based software module for sleep analysis. Choo et al. have demonstrated the potential of PSG autoscoring in reducing the burden of manual scoring by sleep technologists, suggesting operational significance for sleep laboratories in the healthcare setting.

Finally, in this Research Topic, physical therapy through a smartphone application for home-based physical therapy for patients with OSA has been studied (Bui-Diem et al.). This application provides video and in-text tutorials for users to follow at home and a scheduler function to assist the user in organizing the training program, which may improve the efficacy of home-based physical therapy in patients with OSA. Within the same objective, Thai authors have used the Nitra application to study the effectiveness of the first internet-based cognitive behavioral therapy for insomnia (CBT-I) in their country (Theppornpitak et al.). The results of this interventional study confirmed the effectiveness of this first internet-based CBT-I by using the Nitra application for improving sleep efficiency and other sleep parameters in patients with chronic subthreshold to moderate insomnia. Finally, the role of the telemedicine management platform in the management of OSA should be considered. The results of the final study included in this Research Topic demonstrated that CPAP therapy may present distinct trajectories of adherence over time in addition to the traditional binary classification (Yi et al.). Interestingly, this study revealed that self-reported sleep health issues and psychological characteristics might be predictors of different adherence subtypes in patients with OSA. Thus, the authors stated that understanding CPAP use, profiles, and their predictors enable the identification of those who may require additional intervention to improve

adherence and further enhance its therapeutic effect in OSA patients (Yi et al.).

In conclusion, this Research Topic gives an overview of the multidirectional correlation and interaction between sleep disorders and airway diseases. Especially, the application of advanced and revolutionary technologies in the diagnosis and treatment of OSA for personalized management of patients with airway diseases is necessary for the future. We hope that the readers of this Research Topic may benefit from useful information in the emerging field for their clinical practices.

Author contributions

SD-Q: Conceptualization, Validation, Writing—original draft, Writing—review and editing. NC: Conceptualization, Supervision, Validation, Visualization, Writing—review and editing. VN-N: Conceptualization, Validation, Visualization, Writing—original draft, Writing—review and editing. TC: Conceptualization, Methodology, Validation, Visualization, Writing—review and editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Classification of severe obstructive sleep apnea with cognitive impairment using degree centrality: A machine learning analysis

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In this study, we aimed to use voxel-level degree centrality (DC) features in combination with machine learning methods to distinguish obstructive sleep apnea (OSA) patients with and without mild cognitive impairment (MCI). Ninety-nine OSA patients were recruited for rs-MRI scanning, including 51 MCI patients and 48 participants with no mild cognitive impairment. Based on the Automated Anatomical Labeling (AAL) brain atlas, the DC features of all participants were calculated and extracted. Ten DC features were screened out by deleting variables with high pin-correlation and minimum absolute contraction and performing selective operator lasso regression. Finally, three machine learning methods were used to establish classification models. The support vector machine method had the best classification efficiency (AUC = 0.78), followed by random forest (AUC = 0.71) and logistic regression (AUC = 0.77). These findings demonstrate an effective machine learning approach for differentiating OSA patients with and without MCI and provide potential neuroimaging evidence for cognitive impairment caused by OSA.

KEYWORDS

obstructive sleep apnea, resting-state functional magnetic resonance imaging, degree centrality, machine learning, mild cognitive impairment

Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repeated airflow stoppages caused by partial obstruction of the upper airway during sleep, affecting approximately 14% of adult men and 5% of adult women (1, 2). Recurrent upper airway obstruction in OSA patients results in intermittent hypoxia, fragmented sleep, and excessive day-time sleepiness (3). Furthermore, OSA has been shown to be associated with mild cognitive impairment (MCI), especially in older adults (4). Currently, the research on OSA and MCI is still in its infancy; however, there is some evidence suggesting that oxidative stress and endothelial function damage caused by intermittent hypoxia are related to cognitive impairment (5).

However, the neuroimaging mechanisms involved in the association between OSA and MCI are not fully understood, and the assessment of OSA cognitive impairment is challenging to some extent.

With the continuous development of imaging technology, researchers have been involved in the study of MCI, brain function, and brain structure progressively. Reportedly, OSA patients have multiple brain abnormalities related to cognitive dysfunction apparent in regions such the cerebellum, insula, temporal area, and hippocampus (6–9). Resting state functional magnetic resonance (fMRI) reflects brain function under *in vivo* physiological and pathological conditions through resting oxygen-dependent changes. In the resting state, neurons in the brain exhibit spontaneous activity that is transmitted to other neurons, forming a complex network of functions. DC can explore the characteristics of the whole brain functional connection at the voxel level (10), complete the construction of the whole brain functional network, explore the functional community within the functional connection group (11), and avoid the influence of subjective seed point selection. Simultaneously, DC does not require prior prediction, making it more suitable for exploring neural correlations of dimensional and classified phenotypic data (12). Our previous study showed that the DC changes in the bilateral posterior cerebellar, frontal, temporal, and insula lobes before and after CPAP therapy confirmed the high overlap between the reversed brain region and the initial injury brain region, objectively reflecting the effectiveness of CPAP therapy (13). In another Alzheimer's study, patients who recovered from MCI had lower DC in the right lower cerebellum and higher DC in the left superior medial frontal gyrus and left inferior temporal gyrus compared with healthy participants, suggesting that loss of function in local brain structures could be compensated for by enhanced function in surrounding areas (14). Enabled by the high sensitivity and repeatability of DC technology (15), the application of DC to cognitive disability-related diseases to explore the reversible potential physiological mechanism of neural network injury and brain injury has become more frequent (16, 17).

Machine learning is widely used in binary classification because of its parallelism, self-organization, adaptive learning ability, and robustness (18). Common classification methods in data mining and machine learning include artificial neural network, logistic regression (LR), random forest (RF), and support vector machine (SVM)(19–22). Khatri et al. performed diagnostic classification of MCI patients and healthy people based on multimodal MRI (ReHo, fALFF, ALFF, DC) and hippocampal and amygdala volumes, and compared the classification efficiency of various machine learning methods. Eventually, they achieved good classification performance, with SVM as the best classifier (AUC 94.03%, accuracy 92.45%) (23). Bigham et al. used diffusion tensor imaging for diagnostic classification of MCI patients and healthy people in combination with a fast correlation filter for feature screening of high-dimensional data and obtained a good SVM classification feature model with 83.3% accuracy and 80.7% sensitivity (24).

Based on those findings, in this study, we assume that a variety of machine learning methods can be used to construct classification models (including SVM, RF and LR) through DC features, and can effectively identify patients with cognitive impairment from OSA patients. The objectives of this study were as follows: 1. DC was used to detect OSA patients with MCI and OSA patients without MCI, while the LASSO regression method was used to screen out the most characteristic brain regions, 2. A variety of machine learning methods (SVM, LR and LR) were compared simultaneously to build the optimal performance model.

Material and methods

All OSA patients were diagnosed with obstructive sleep apnea in the sleep monitoring room of the First Affiliated Hospital of Nanchang University's Department of Respiratory Medicine, between August 2017 and June 2022. The diagnosis of all patients was jointly determined by experienced respiratory physicians in accordance with the guidelines of the American Academy of Sleep Medicine (AASM) 2017 Clinical Practice Guidelines for adult obstructive sleep apnea (25). Inclusion criteria were as follows: apnea hypopnea index (AHI) > 15/h; All participants were right-handed, native Chinese speakers and aged 20 to 60. Exclusion criteria were as follows: (1) Sleep disorders other than OSA (e.g., insomnia, drowsiness); (2) Respiratory diseases, cardiovascular diseases, diabetes mellitus, hypothyroidism, central nervous system diseases, trauma, and other conditions that would explain an AHI > 15/h independent of OSA; (4) Alcohol or illicit drug abuse or current use of psychotropic substances; (4) Contraindications to MRI, such as claustrophobia; (5) Image artifact. A final 99 OSA patients were included in the analysis. We abide by the principles of the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University [2020(94)]. Participants signed written informed consent documentation for this study.

Research framework

Our research framework is shown in Figure 1 and the specific steps are as follows:

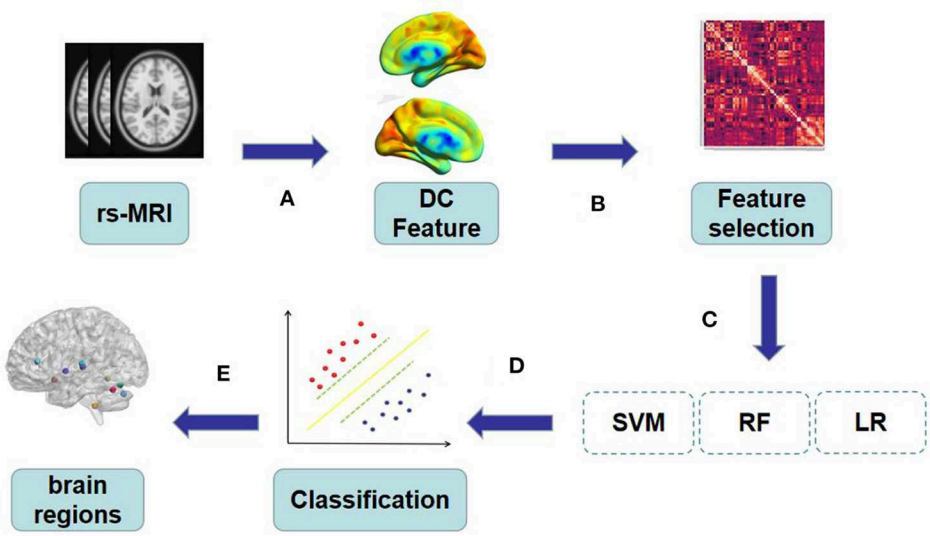

FIGURE 1
(A) The original rs-MRI was preprocessed and regions of interest were extracted by AAL template as features. **(B–C)** All the features extracted from DC were screened for feature correlation, and the minimum absolute contraction and Selection operator logic method was used for 10-fold cross verification to retain the features with non-zero coefficients. **(D)** The extracted features are trained by SVM, RF and LR to obtain the best model. **(E)** Visual mapping of brain regions according to the characteristics of the best model.

Polysomnography and neuropsychological assessment

Prior to polysomnography (PSG) monitoring, all participants were asked not to consume alcohol or coffee. All participants received an overnight PSG (from 10 p.m. to 6 a.m.), using the Respironics LE physiological monitoring system of (Alice 5 LE, Respironics, Orlando, FL, USA). PSG monitoring includes standard electrocardiogram, electro-ophthalmogram, electromyogram, electrocardiogram, body position, nasal and oral airflow, chest and abdominal respiratory movement, snoring, etc. Saturation of pulse oxygen (SpO_2), sleep latency, total sleep time, sleep efficiency, sleep stage, awakening, and respiratory events were recorded (26). Obstructive apnea is described as a continuous 90% reduction in airflow, lasting > 10 seconds, with significant dyspnea. The apnea index (AHI) is the sum of apnea and hypopnea events occurring per hour during sleep.

All participants completed the MoCA cognitive scale assessment in a quiet state under the guidance of a professional neuropsychologist. Cognitive function was assessed using 11 MoCA items, which were examined in eight cognitive domains, including executive function, language, attention, computation, abstraction, naming, memory, and orientation. A MoCA score < 26 indicates cognitive impairment (27).

MRI data acquistion

MRI images were collected for all participants in a 3.0 Tesla MRI scanner in our hospital's 8-channel phased array head coil (Siemens, Munich, Germany). Foam pads were used to reduce the patient's head movement, and earplugs were used to reduce scanner noise. Before the scan, all participants were required to close their eyes, stay awake and not engage in specific thinking activities. First, conventional MRI scan was performed, and conventional T1-weighted imaging was performed: Repetition time (TR) = 250 ms, echo time (TE) = 2.46 ms, Thickness = 5 mm, clearance = 1.5 mm, FOV = 220 x 220 mm, TR= 4,000 ms, TE = 113 ms, thickness = 5 mm, Clearance = 1.5 mm, FOV = 220 × 220 mm, slice = 19). Then, high-resolution T1-weighted MRI images of brain structures were obtained from each subject using brain volume sequences on the sagittal plane (TR = 1,900 ms, TE = 2.26 ms, thickness = 1.0 mm, gap = 0.5 mm, FOV = 250 × 250 mm, Matrix = 256 × 256, turn Angle = 9, slice = 176). Finally, in the axial plane (TR = 2,000 ms, TE = 30 ms, turn Angle = 90, thickness = 4.0 mm, clearance = 1.2 mm, rs-fMRI data), field of view = 230 × 230 mm 2, matrix size = 64 × 64, slice = 30), a total of 240 rs-fMRI images were recorded. Two experienced radiologists read the images to exclude lesions and motion artifacts visible to the naked eye.

Data pre-process

Imaging data were examined with MRIcro software (www.MRIcro.com) to discard suboptimal data. Data were obtained from resting state using the Data Processing & Analysis for Brain Imaging toolkit (DPABI, Chinese Academy of Sciences, Beijing, China, http://rfmri.org/dpabi), based on statistical parameter mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and MATLAB2018b (Math Works, Natick, MA, USA). First, the file format was converted from DICOM to NIFTI. Then, time layer correction and 3D head motion correction were carried out for the remaining time series. Participants with frame displacement > 2.5 standard deviations were excluded (28). Linear transformation was used to co-register structural images with functional images of each subject. Therefore, the new segmentation in SPM12 was used to segment structural images of all participants into white matter and cerebrospinal fluid. Then, the image space was normalized to the Montreal Neurological Institute (MNI) template and resampled to $3 \times 3 \times 3$ mm^3 voxels. Finally, linear regression was used with regression Friston 24 parameters, white matter signals, and cerebrospinal fluid signals from all voxel time series, after filtering using a time filter (0.01–0.08 Hz). Please refer to our previous study for more details (29).

Voxel-level degree centrality

The default whole-brain gray matter template ($61 \times 73 \times 61$, 3 mm × 3 mm × 3 mm, 67,541 voxels) was extracted using DPABI software. Pearson correlation coefficients between arbitrary voxels of each subject are calculated in the default gray matter template. DC between voxels was calculated according to the following formula (10):

$$Dc(i) = \sum_{j=1}^{N} rij(rij > r0)$$

The correlation coefficient between voxel i and voxel j is expressed as r_{ij}, and the correlation threshold used to eliminate weak correlation is called r0 (30). Then Fisher transform was used to transform the correlation coefficient into z-score graph to improve the normality. Finally, gauss was used to check the z-score graph with the maximum half-width and height of 6 mm for smoothing.

Feature extraction and feature selection

After rs-fMRI data pretreatment, zDC of each brain region of the zDC map obtained by us were extracted based on automatic anatomical labeling (AAL) map (31), and 116 brain regions were selected as features.

Firstly, Pearson's correlation coefficient between each group of features was calculated, and 0.75 was set as the absolute correlation threshold. For feature pairs whose correlation was greater than the threshold value, the variables with higher average absolute correlation were deleted after comparing their average absolute correlation, weakening multicollinearity at a small cost. Then, we used the least absolute shrinkage and selection operator (LASSO) logic method for 10-fold cross validation (32), Alpha was searched in the range of 10^{-6} to 10^3, with a step size of $10^{0.2}$, and the optimal Alpha value was selected as a cost function using the mean square error (MSE). Finally, non-zero coefficient features were selected to train the classification model. Feature selection is performed in Python 3.8.8 using the software package "scikit-learn" (33).

SVM

SVM is a supervised learning technique for partitioning and classification by searching for the optimal hyperplane. The algorithm was originally designed to solve the problem of binary classification. It has good generalization ability, can avoid dimensional disaster, and is widely used in neuroimaging and disease classification (34, 35).

RF

RF is a comprehensive learning algorithm that uses multiple decision trees for prediction. It is a vote on the predicted results of all decision trees (36). The variance of the model can be effectively reduced by constructing the training set with random sampling so that each feature is a part of the whole feature vector.

LR

The LR is a supervised machine learning classifier that predicts the likelihood of a target variable (37). This multivariable technique seeks to establish a functional relationship between many predictive variables and a single output. LR is a powerful maximum likelihood algorithm that can use discrete and continuous data sets to generate probabilities and classify new data.

Classification

We construct three representative machine learning classification models, namely SVM, RF, and LR models, respectively. GridSearchCV is used for hyperparameter optimization, and a Leave-one-out cross-validation method and permutation test (5000 times) are used for model performance verification. We calculated the accuracy, sensitivity, and

TABLE 1 General clinical scale.

	MCI ($n = 51$)	nMCI (n = 48)	P value
Sex (M/F)	48/3	47/1	0.654
Age (year)[a]	38.47 ± 7.93	35.45 ± 8.76	0.076
Education (year)[b]	12.98 ± 2.33	13.78 ± 3.21	0.163
BMI (Kg/m^2)[a]	27.26 ± 3.06	26.78 ± 4.20	0.514
Neck circumference (cm)[b]	41.17 ± 3.24	39.95 ± 2.77	0.048
Waistline (cm)[b]	99.19 ± 6.92	97.04 ± 15.18	0.361
AHI[a]	53.19 ± 23.12	49.58 ± 19.23	0.402
Nadir SpO_2 (%)[b]	71.25 ± 12.52	68.31 ± 12.52	0.244
$MSpO_2$ (%)[b]	92.38 ± 3.57	91.82 ± 5.13	0.530
Total sleep time (min)[b]	366.05 ± 112.36	379.20 ± 77.78	0.503
Sleep efficiency (%)[b]	80.01 ± 22.20	85.74 ± 12.14	0.118
N1(%)[b]	28.94 ± 17.26	25.16 ± 16.58	0.270
N2(%)[b]	39.32 ± 12.68	43.16 ± 15.09	0.174
N3(%)[b]	19.58 ± 14.68	21.39 ± 15.68	0.555
REM(%)[b]	15.45 ± 9.90	12.63 ± 8.71	0.137
$SpO_2 < 90\%$[b]	24.34 ± 20.02	23.23 ± 16.36	0.764
MoCA[b]	22.23 ± 2.61	27.27 ± 1.16	<0.001

MCI, mild cognitive impairment; nMCI, no mild cognitive impairment; AHI, apnea hypopnea index; Nadir SpO_2, minimum saturation of pulse oxygen; $MSpO_2$, average saturation of pulse oxygen; REM, rapid eye movement; $SpO_2 < 90\%$, percentage of total sleep time with oxygen saturation < 90; [a], Student, t-test; [b], Mann-Whitney U-test.

specificity of different models, and used the receiver operating characteristic (ROC) curve and area under the curve (AUC) to evaluate the performance of the models. The optimal model was selected, and Cohen's Kappa was used to evaluate the heterogeneity of test results. All selected DC features are weighted to quantify their contribution to the model.

Statistics

For the demographic and clinical evaluation data, SPSS 23.0 software was first used for processing, and kolmogorov-Smirnov was used to test the normality of the data. Then, two-sample t-test was performed on the data conforming to normal distribution, and Mann-Whitney U test was performed on the non-normal distribution data. $P < 0.05$ was considered statistically significant. Chi-square test was adopted for the data of dichotomous variables, and $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics

Summary of demographic and clinical characteristics of OSA patients in MCI group and nMCI group (Table 1).

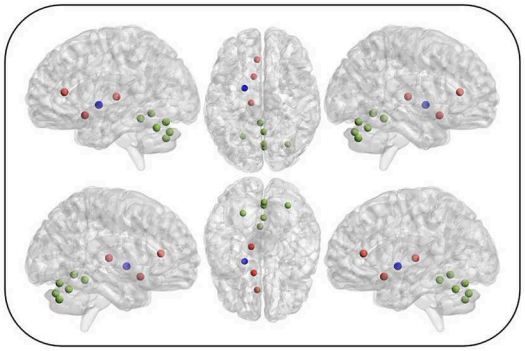

FIGURE 2
Red represents the default mode network; Blue represents the basal node network; Green represents the cerebellum network.

We found that there were significant differences in neck circumference and MoCA scale between MCI group and nMCI group, $P < 0.05$. There were no significant differences in age, education, BMI, waist circumference, AHI, Nadir SpO_2, mean SpO_2, Total sleep time, N1, N2, N3, $SpO_2 < 90\%$, sleep efficiency and REM between the two groups ($P > 0.05$).

Feature selection

Between MCI and nMCI groups, we finally obtained 10 DC features through feature selection procedures, as shown in Figure 2, Table 2.

Classification efficiency

After the above feature screening method, 10 brain region DC features were selected, and the performance comparison of the three machine learning models was obtained after hyperparameter optimization and retention cross-validation, as shown in Table 3, Figure 3. The accuracy of SVM model was 0.71 and AUC was 0.78(sensitivity = 82.35%, specificity = 60.42%, p-value 0.0026 after 5,000 permutation tests), which showed better performance than the other two models.

Discussion

In this study, we extracted DC from the whole brain as a selection feature and combined it with a variety of machine learning methods (SVM, LR, RF) to train a classifier. We found that SVM had the best classification performance to distinguish OSA patients with cognitive impairment. Simultaneously, we also used LASSO to select the most discriminating brain regions

TABLE 2 The selected DC features set for discriminating the MCI from nMCI group.

ID	Feature	Brain Network	MCI		nMCI		Weight		
			Mean	SD	Mean	SD	SVM	LR	RF
1	Olfactory R	DMN	−0.095	0.292	−0.187	0.245	0.45695206	0.61365026	0.07962183
2	Cingulum Ant L	DMN	0.174	0.336	0.293	0.385	−0.45212804	−0.41221711	0.08364737
3	Pallidum L	Basal node network	−0.11	0.383	0.088	0.477	0.03777478	−0.02233599	0.07402411
4	Transverse temporal L	DMN	0.26	0.412	0.489	0.351	−0.28568111	−0.3511914	0.10909707
5	Cerebelum Crus1 R	Cerebellum network	0.059	0.280	−0.088	0.289	0.57115715	0.49502768	0.10136584
6	Cerebelum 4 5 L	Cerebellum network	−0.027	0.221	0.151	0.239	−0.3993657	−0.3675441	0.17269695
7	Vemis 1	Cerebellum network	−0.386	0.348	−0.258	0.272	−0.14545911	−0.44863276	0.09362268
8	Vemis 6	Cerebellum network	−0.123	0.280	0.001	0.335	−0.47500579	−0.24829838	0.07821442
9	Vemis 8	Cerebellum network	−0.419	0.310	−0.286	0.295	−0.37868619	−0.58716901	0.11912403
10	Vemis 10	Cerebellum network	−0.399	0.304	−0.503	0.284	0.56859686	0.84123316	0.08858571

DMN, default mode network; MCI, mild cognitive impairment; nMCI, no mild cognitive impairment; SVM, support vector machine; LR, logistic regression; RF, random forest.

TABLE 3 Classification performance of machine methods.

	AUC	Accuracy	Sensitivity	Sepecificity	Kappa
SVM	0.78	0.71	0.82	0.60	0.47
RF	0.71	0.70	0.62	0.79	0.42
LR	0.77	0.71	0.84	0.58	0.43

SVM, support vector machine; RF, random forest; LR, logistic regression.

used to distinguish MCI from nMCI, including the olfactory cortex, cingulate gyrus, globus pallidus, transverse temporal gyrus, cerebellum and other regions, providing more evidence to explain the heterogeneity and complexity of OSA patients with cognitive impairment.

Machine learning

Due to the overall scarcity and financial burden of PSG, methods combining multidimensional clinical parameters and machine learning have been widely used to distinguish OSA, OSA severity, and OSA prognosis (2, 38, 39). However, studies using DC to distinguish OSA are relatively rare. Yujun Gao et al. (40) showed that compared with healthy people, changes in DC values of right superior frontal gyrus, hippocampus, superior temporal gyrus and caudate nucleus in epileptic patients can be distinguished with high precision between epileptic patients and healthy controls by combining SVM model, and the unique DC model can be used as an imaging marker for the diagnosis of epilepsy. Chang Xi et al. used whole-brain voxel level DC combined with machine learning to distinguish major depression and bipolar disorder. The DC reduction of default mode network and sensorimotor network can be used as an effective feature to distinguish depression, and the DC-based classification model has a high accuracy (91%) (41). These studies suggest that changes in DC can be used as neuroimaging markers to distinguish cognitive dysfunction.

LASSO is efficient for feature selection, avoiding data redundancy while preserving the most discriminating important features (42). Features were reduced according to LASSO, and the addition of reduction can improve model performance in partitioned OSA patients with and without MCI by avoiding overfitting and miscalibration. Altogether, among all the classifiers, the performance of SVM classifier is significantly better than other classifiers. Yu Zhou et al.(43) showed that the extraction of the white matter connection network in the hippocampus was used as an effective feature to classify the MCI group of AD patients and the healthy control group, SVM rbf classification efficiency (ACC = 89.4%, AUC = 0.954) was better than KNN (ACC = 86.9%, AUC = 0.920) and RF (ACC = 84.8%, AUC = 0.935). Based on DC features, this study uses three machine learning techniques to generate classification models, namely SVM, LR and RF. Since this study relied on a small data set, to obtain more sufficient data training, we adopted the keep-one method to test the model performance. Finally, SVM had the best classification performance (accuracy = 71%, AUC = 0.78), RF (accuracy = 70%, AUC = 0.71), LR (accuracy = 71%, AUC = 0.77). At the same time, linear kernel SVM can extract the weight of each feature and reflect the importance of each feature in the model.

DC feature

The characteristics of screening between MCI and nMCI groups mainly involve the default network, basal ganglia area network, and cerebellar network. The DMN consists of discrete and bilaterally symmetric cortical regions, mainly involving the

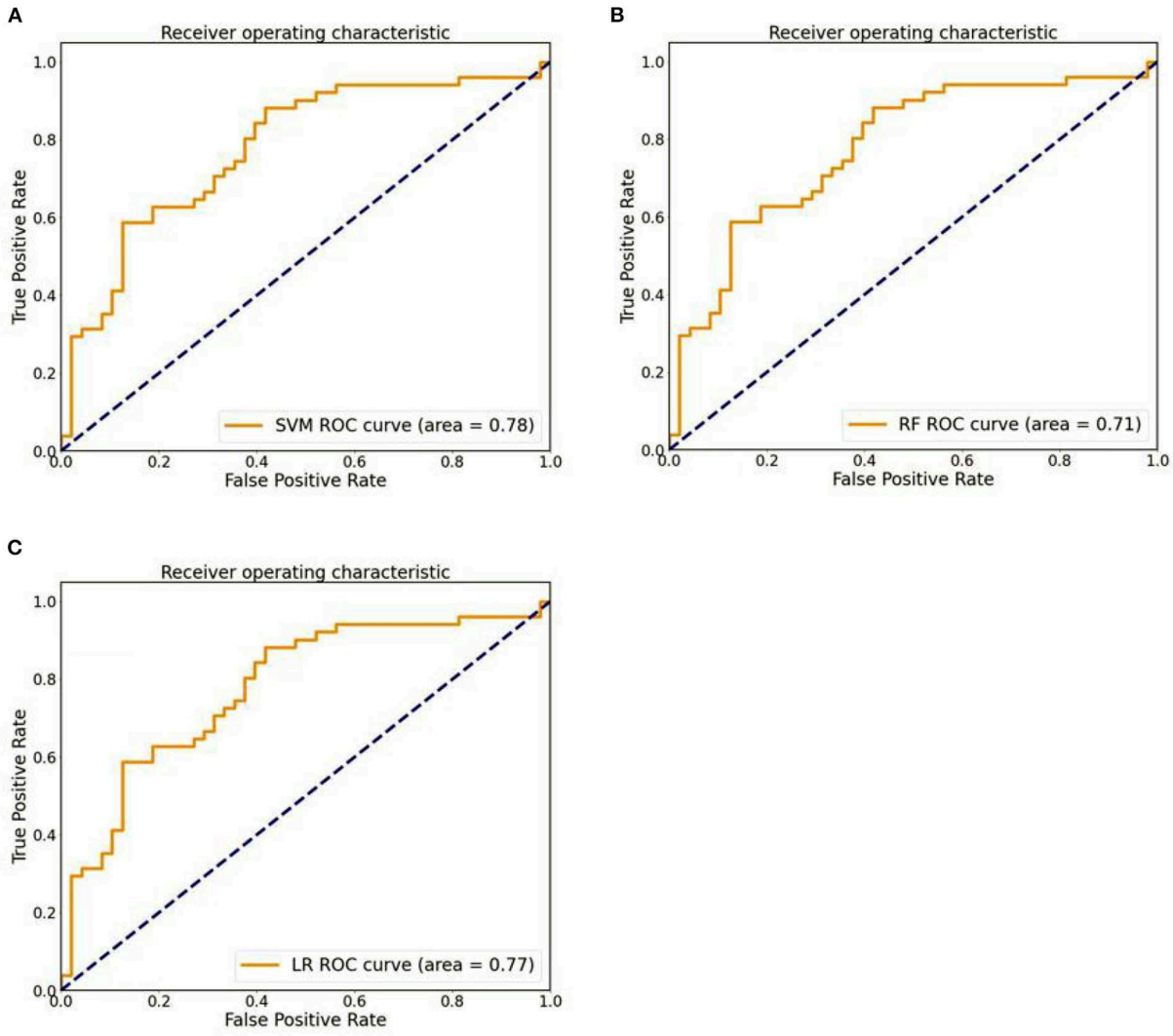

FIGURE 3
(A) The ROC curves of SVM models. **(B)** The ROC curves of RF models. **(C)** The ROC curves of LR models.

anteromedial frontal, temporal, and parietal cortex regions, and is characterized by high activity when the brain is not involved in tasks (44). Abnormal activity of the DMN is associated with cognitive function and symptoms of neuropsychiatric diseases (45, 46), and its functional changes have also been confirmed in relevant studies on OSA (47). Our previous study showed (48) that, based on the graph theory approach, DMN topological abnormalities in OSA patients were associated with cognitive dysfunction, especially memory delay and memory retrieval. Prilipko et al. showed that functional inactivation of the DMN region in OSA patients was significantly related to behavioral performance and episodic memory compared with the healthy group (49). These studies suggest that abnormal functional changes in the DMN may be one of the most effective markers to distinguish OSA patients with concomitant MCI.

The globus pallidus is one of the components of the basal ganglia and is involved in the final output of direct and indirect pathways of the basal ganglia network, and its impairment can cause a variety of cognitive and motor problems (50). Previous studies have confirmed that globus pallidus neurons have higher energy requirements and are more susceptible to oxygen deprivation than other neurons in the basal ganglia region (51). Oxidative stress is also one of the important factors of neuron degeneration in the basal ganglia (52). A study on the structure of the basal ganglia region found morphological changes in the left globus pallidus and thalamus in children with OSA (53), which is helpful for understanding the autonomic activity and respiratory muscle activity abnormalities caused by OSA-related dysfunction of the globus pallidus. Our findings suggest that DC differences in the globus pallidus contribute to

our understanding of the neuroimaging mechanisms by which OSA leads to cognitive dysfunction, which may help distinguish OSA from MCI.

The cerebellum and extra-cerebellar structures have extensive connections in motor and non-motor aspects. The cerebellum is not only involved in motor control, but also in cognitive and affective processing (54), which is based on the anatomical basis that there are multiple parallel circuits in the cerebellum and the cerebral cortex that are widely interconnected (55). Previous studies have shown that OSA can lead to significant changes in the structure and function of cerebellum (56), and lack of sleep is also a risk factor for damaging cerebellum function (57). Our previous studies have shown increased intrinsic connectivity in the right posterior cerebellar lobe in OSA patients prior to treatment, which may be a functional compensation for chronic intermittent hypoxia (6). It has been proposed that changes in the internal function of the cerebellum can be used as a model to predict motor and cognitive tasks (58). Therefore, we believe that neuroimaging changes in the cerebellar network may be one of the effective markers for identifying OSA with cognitive impairment.

Limitation

The current study has some limitations. First, the sample size was relatively small and there was no external data set to verify to improve the generalization ability of the model. Secondly, most of our participants were male OSA patients with severe OSA, which may not be applicable to OSA patients with mild OSA or female OSA patients. Finally, we discuss only one fMRI functional feature, which will be combined with other fMRI features (functional connectivity, gray matter volume) and highly relevant clinical features (such as hyperlipidemia) to improve the classification efficiency of the model in the future.

Conclusion

Our results demonstrate an effective machine learning approach that uses DC as a feature to effectively identify OSA patients with concomitant cognitive impairment. This study helps us better understand the neuroimaging mechanisms of OSA causing cognitive impairment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of the First Affiliated Hospital of Nanchang University [2020(94)]. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XL and YS wrote, reviewed, and revised the manuscript. DP guided and designed the MRI experiment. HL analyzed the resting-state fMRI data. XL and HL analyzed and discussed the ideas of the paper. PY analyzed machine learning. WD, KL, YZ, and WX collected resting-state fMRI data and applied for the ethics approval. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy of obstructive sleep apnea treatment by antileukotriene receptor and surgery therapy in children with adenotonsillar hypertrophy: A descriptive and cohort study

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Background: Prevalence of obstructive sleep apnea (OSA) in children with adenotonsillar hypertrophy is high and related to the occlusion of the upper airway. The main treatments of OSA in these children is adenotonsillectomy. However, this intervention is an invasive method with a various success rate. Thus, the indications of tonsillectomy remain debatable and non-invasive treatment is still a potential choice in these patients.

Methods: It was a cross-sectional and interventional study. This study included children aged from 2 to 12 years-old who were diagnosed with OSA by respiratory polygraphy and had tonsillar hypertrophy with/without adenoid hypertrophy. All main data including age, gender, height, weight, body mass index (BMI), clinical symptoms, and medical history were recorded for analysis. Physical examination and endoscopy were done to evaluate the size of tonsillar and adenoid hypertrophy by using Brodsky and Likert classifications, respectively. The severity of OSA was done by using the classification of AHI severity for children.

Results: There were 114 patients (2–12 years old) with a mean age of 5.5 ± 2.1 years included in the present study. The main reasons for consultations were snoring (96.7%), a pause of breathing (57.1%), an effort to breathe (36.8%), unrefreshing sleep (32%), doziness (28.2%), and hyperactivity (26.3%). There were 36% of subjects with tonsillar hypertrophy grade 1–2, 48.2% with grade 3, and 15.8% with grade 4 (Brodsky classification); among them, there were 46.5% of subjects with grades 1–2 of adenoid hypertrophy, 45.6% with grade 3, and 7.0% with grade 4 (Likert classification). The mean AHI was 12.6 ± 11.2 event/h. There was a significant correlation between the mean AHI and the level of tonsillar and adenoid hypertrophy severity ($r = 0.7601$ and $r = 0.7903$; $p < 0.05$ and $p < 0.05$, respectively). The improvement of clinical symptoms of study subjects was found in both groups treated with ALR (antileukotriene receptor) or ST (surgery therapy). The symptoms related to OSA at night

including snoring, struggle to breathe, sleeping with the mouth open, and stopping breathing during sleep were significantly improved after treatment with ATR and with ST ($p < 0.001$ and $p = 0.001$, respectively). The mean AHI was significantly reduced in comparison with before treatment in study subjects treated with ALR (0.9 ± 1.0 vs. 3.9 ± 2.7 events/h; $p = 0.001$) or with ST (3.5 ± 1.4 vs. 23.4 ± 13.1 events/h; $p < 0.001$).

Conclusion: The treatment of OSA due to adeno-tonsillar hypertrophy with ALR for moderate OSA or surgery for severe OSA might reduce the symptoms related to OSA at night and during the day.

KEYWORDS

adenotonsillar hypertrophy, OSA, apnea-hypopnea index, snoring, antileukotriene receptor, adenotonsillectomy

Introduction

Obstructive sleep apnea (OSA) is a complete or partial obstruction of the upper airway during sleep and leads to intermittent hypoxia, the creation of oxidative stress, and fragmented sleep (1, 2). OSA can be found in adults, children, and infants (3). The prevalence of OSA in childhood is ∼1–4% and depends on diagnostic criteria (4). Significantly, the prevalence of pediatric OSA has two peak periods. The first peak occurs in children between 2 and 8 years with enlarged tonsils and adenoids. The second peak appears during adolescence with weight gain (5).

OSA can lead to dire health consequences and a significant economic burden without prompt diagnosis and treatment (6). Children with OSA can have central nervous system disturbances such as attention deficit hyperactivity, depression, lack of concentration, and excessive daytime sleepiness (7). In addition, children with OSA have reported for risk of long-term cardiovascular consequences, including hypertension, arrhythmia, abnormal ventricular morphology, impaired ventricular contractility, and elevated right heart pressure (8, 9). Evenly, OSA can lead to death in children, especially sudden death at night (10).

The choice of OSA treatment will depend upon age, clinical symptoms, comorbidities, risk factors, and polysomnography (PSG) results (11). Because in children, tonsillar and adenoid hypertrophy is a major cause of OSA, most children can be treated with surgical adenotonsillectomy (12). However, children reveal a high risk for postoperative complications and the effects of long-term tonsillectomy on the immune system (13, 14). Therefore, pharmacologic therapy can be considered to initiate mild to moderate OSA. Interestingly, tonsillar tissue from children with OSA was reported to overexpress CysLT1, so some RCT applied montelukast for treatment. These reports showed improvement in the severity of OSA and adenoidal hypertrophy in children with non-severe OSA (15–17).

Therefore, the present study was conducted to evaluate the clinical efficacy of antileukotriene drugs and adenotonsillectomy in OSA children with tonsillar hypertrophy.

Methods

Subjects

There were 114 children from 3 to 12 years old included in the present study from August 2016 to December 2019 in National Pediatric Hospital in Vietnam. The present study was approved by the Ethical Committee of Hanoi Medical University and National Pediatric Hospital (No 99/HDDD-DHYHN).

Inclusion criteria

Children having all the following criteria were included in the present study: tonsillar hypertrophy, OSA defined by AASM (American Academic of Sleep Medicine), aged from 3 to 12 years old, and agreement from patients and their guardians.

Exclusion criteria

Children having one of the following criteria were excluded from the study: cranial-facial abnormal structure, Down syndrome, Pierre-Robin syndrome, Treacher Collin syndrome, micro crania, other disorders of the upper airway, neuro-muscular junction disorder such as myasthenia gravis, coagulopathy, renal failure, heart failure, or disagreement from patients and their guardians. All children currently treated with corticosteroids (oral, inhaled or intranasal form) or antihistamines (oral form) or nasal decongestants were also excluded from the study. Patients under antileukotriene therapy with increasing symptoms and refusing surgical treatment were also excluded from the present study.

Methods

Study design

It was a cross-section study; all study subjects with tonsillar hypertrophy received medical treatment if they had a mild-moderate OSA (Group 1) or surgical treatment if they had severe OSA (Group 2); those who were unresponsive to medical treatment after 1 month also received surgical treatment (Group 3; Figure 1). To avoid the bias, OSA children with comorbidities or who were not adherent to antileukotriene therapy during follow-up (monthly) were also excluded from the study. The compliance of antileukotriene therapy was evaluated monthly for each study subject.

Respiratory polygraphy

OSA was defined with polygraphy by using the apnea – hypopnea index (AHI) to classify the severity of OSA as recommended: normal (non-OSA): AHI $\leq$ 1/h; mild OSA: 1/h $<$ AHI $\leq$ 5/h; moderate OSA: 5/h $<$ AHI $\leq$ 10/h; severe OSA: AHI $>$ 10/h (18, 19). Polygraphy was done with Apnea Link (ResMed; San Diego, California, USA).

Tonsillar and adenoid hypertrophy evaluation

Tonsillar hypertrophy was defined by using Brodsky's grading scale (20). There are 5 levels of tonsil hypertrophy based on the ratio of tonsil to the pharynx (distance between two anterior pillars), including grade 0 (located in the cavity), grade 1: occupied $<$ 25% of the distance between the two anterior pillars, grade 2 /3/ and 4: occupied 25–50%/ 50–75%/ and $>$ 75% of the distance between the two anterior pillars, respectively.

Adenoid hypertrophy was defined by Likert's classification (21). There are 5 levels of adenoid hypertrophy based on the occlusion of posterior nasal aperture, including grade 1: occluded from 0 to 25%, grade 2: occluded from 25 to 50%, grade 3: occluded from 50 to 75%, and grade 4: occluded $>$ 75% of posterior nasal aperture.

Data collection

All data on age, gender, height, weight, BMI, medical and family history, clinical characteristics, PSQ (Pediatric Sleep Questionnaire) scores, Mallampati classification, SSS (snoring severity scale) scores, and PG parameters (AHI, SpO2, pulse, and frequency of snoring) of the study subjects were collected for statistical analyses.

Statistical analysis

Epidata and Stada 15 were used to analyze the recorded data. Continuous variables were presented as mean $\pm$ standard deviation (SD). Skewness-Kurtosis test was used for evaluating the normal distribution and Kruskal–Wallis test was done for performing the pairwise comparison. Multiple regression analysis was performed to measure the correlation between AHI and continuous variables with coefficient R of Pearson for normal distribution or Spearman for non-normal distribution variables.

Results

Clinical characteristics and respiratory features of study subjects

There were 114 patients (2–12 years old) with a mean age of 5.5 $\pm$ 2.1 years included in the present study. The gender rate was 3.1/1 (male/female) (Table 1A). The percentage of subjects in the age group of 3–8 years old was 75.5% and underweight was 27.2%. For medical history, there was 33.2% of patients had allergic rhinitis, 11.2% of asthma, and 68.4% with a family history of snoring (Table 1A).

The main reasons for consultations were snoring (96.7%), a pause of breathing (57.1%), an effort to breathe (36.8%), unrefreshing sleep (32%), doziness (28.2%), hyperactivity (26.3%), loss of concentration (17.5%), daytime sleepiness (14.9%), nasal congestion nose at night (13.2%), and wake up during sleep (12.3%) (Table 1A).

ENT examination showed that 36% of subjects with tonsillar hypertrophy grade 2, 48.2% with grade 3, and the most common age was from 3 to 8 years old (75.4%). There were 46.5% of subjects with grades 1–2 of adenoid hypertrophy and 45.6% with grade 3 (Table 1A). The classification of tonsillar and adenoid hypertrophy severity was presented in Table 1B.

Respiratory polygraphy of study subjects showed that the average apnea hypopnea index (AHI) was 12.6 $\pm$ 11.2 event/h; the lowest oxygen saturation was 75.7 $\pm$ 13.7%, and the number of events of snoring was 426.3 $\pm$ 315.9 (Table 1A). There was an increasing and significant correlation between the mean AHI and the level of tonsillar and adenoid hypertrophy severity (r = 0.7601 and r = 0.7903; $p < 0.05$ and $p < 0.05$, respectively; Figure 2).

Characteristics of study subjects classified by treatments

The results showed that subjects treated with surgical therapy (ST) were younger and had higher BMI than those treated with anti-leukotriene receptors (ALR) (4.9 $\pm$ 1.9 and 17.7 $\pm$ 3.6 vs. 5.9 $\pm$ 2.1 years and 16.4 $\pm$ 2.8 kg/m^2; $p = 0.004$ and $p =$

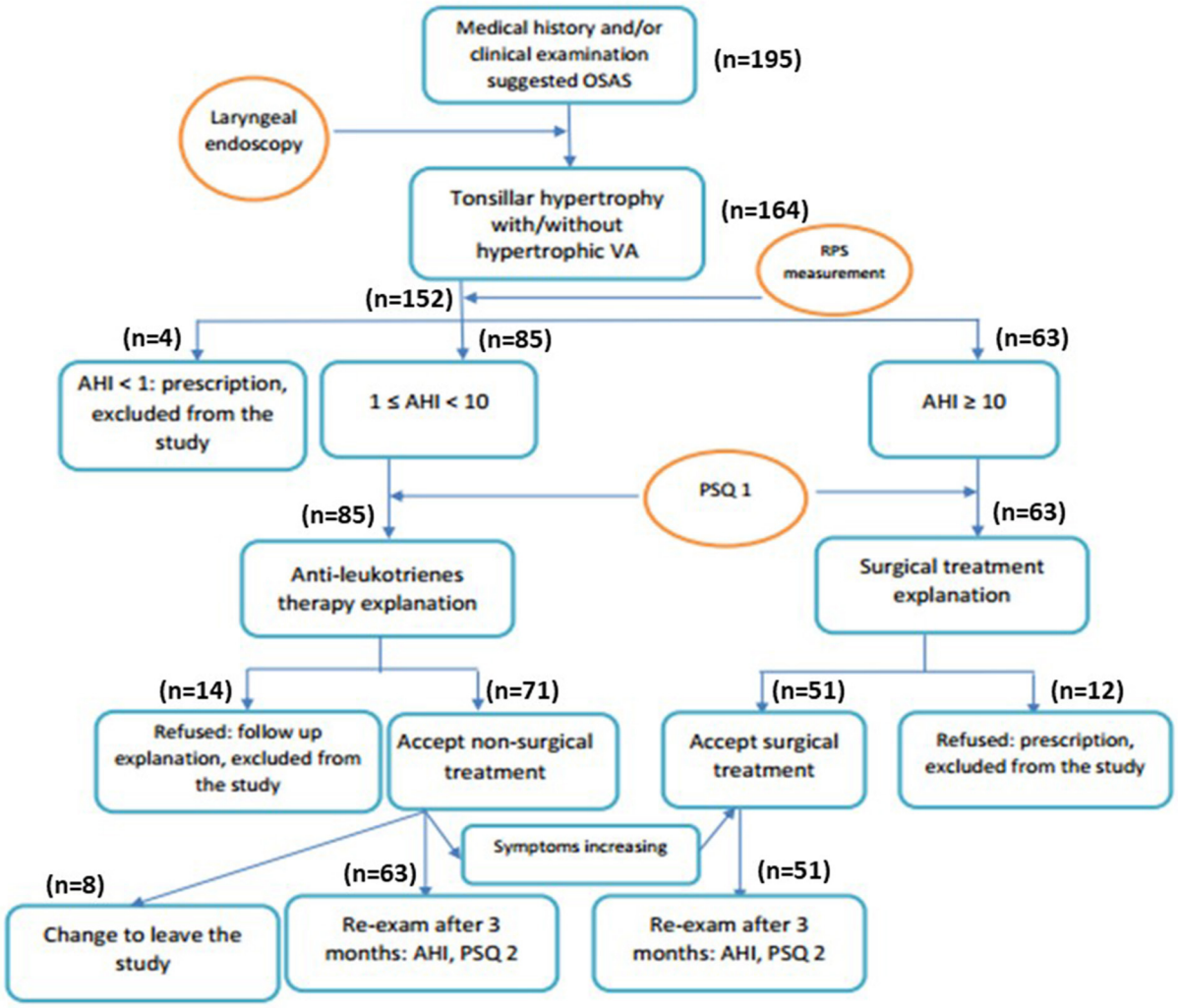

FIGURE 1
Flow-chart of study process. AHI, apnea-hypopnea index; PSQ, pediatric sleep quality; RPS, respiratory polysomnography.

0.030; respectively; Table 2). There was no significant difference in gender between the two groups (Table 2).

The mean AHI of study subjects treated with ST for adenotonsillar hypertrophy was higher than that in study subjects treated with ALR (23.4 ± 13.1 vs. 3.9 ± 2.7 and <0.001; Table 2). The percentage of severe OSA in study subjects treated ST group was significantly higher than those treated with ALR (86.2 vs. 0.0%; $p < 0.001$). There was 74.6% of mild OSA and 25.4% of moderate OSA in study subjects treated with ALR (Table 2). The mean SpO2 in the OSA period of subjects treated with ST was significantly lower than those treated with ALR (74.2 ± 13.9% vs. 86.0 ± 8.8% and $p = 0.001$. There were not any significant differences in nadir SpO2 and snoring events between the two groups (Table 2).

Clinical improvements of treatments in study subjects

The improvement of clinical symptoms of study subjects with OSA was found in both groups of treatment with ALR and ST (Table 3). The symptoms related to OSA at night including snoring, struggle to breathe, sleeping with the mouth open, and stopping breathing during sleep were significantly improved after treatment with ATR and with ST ($p < 0.001$ and $p = 0.001$, respectively; Table 3).

The results of the present study showed that the daytime symptoms due to the consequences of OSA such as breathing by mouth, daytime sleepiness, difficulty sustaining attention in tasks, failure of attention to details, loss of things (toys, pencils...), or easily distracted by extraneous stimuli were

TABLE 1A Clinical characteristics and respiratory polygraphy features of study subjects.

Parameters	Study subjects ($n = 114$)		Parameters	Study subjects ($n = 114$)	
	Mean ± SD	*n* (%)		Mean ± SD	*n* (%)
Age, years	5.5 ± 2.1	-	**Tonsillar hypertrophy**		
BMI, kg/m^2	16.9 ± 3.2	-	Grade 1–2	-	41 (36.0)
Gender			Grade 3	-	55 (48.2)
Male	-	75.4	Grade 4	-	18 (15.8)
Female	-	24.6	**Adenoid hypertrophy**		
Main reason of consultation			Grade 1–2	-	54 (46.5)
Snoring	-	96.7	Grade 3	-	52 (45.6)
Pause of breathing	-	57.1	Grade 4	-	8 (7.0)
Effort to breath	-	36.8	**Respiratory polygraphy**		
Unrefreshing sleep	-	32.0	AHI (event/h)	12.6 ± 11.2	-
Doziness	-	28.2	Mild	-	48 (42.1)
Hyperactivity	-	26.3	Moderate	-	22 (19.3)
Loss of concentration	-	17.5	Severe		44 (38.6)
Daytime sleepiness	-	14.9	SpO2 in the OSA period	80.6 ± 12.8	-
Nasal congestion at night	-	13.2	Nadir SpO2	75.7 ± 13.7	-
Wake up during sleep	-	12.3	Number event of snoring	426.3 ± 315.9	-

BMI, body mass index; AHI, apnea-hypopnea index.

TABLE 1B The classification of tonsillar hypertrophy and adenoid hypertrophy by age group.

Age group	Tonsillar hypertrophy severity			Total *N* (%)	Adenoid hypertrophy severity			Total *N* (%)
	Grade 1+2 N (%)	Grade 3 N (%)	Grade 4 N (%)		Grade 1+2 N (%)	Grade 3 N (%)	Grade 4 N (%)	
<3 years	3 (18.8)	10 (62.5)	3 (18.8)	16 (100.0)	4 (25.0)	8 (50.0)	4 (25.0)	16 (100.0)
3–5 years	6 (18.8)	20 (62.5)	6 (18.8)	32 (100.0)	12 (37.5)	18 (56.2)	2 (6.3)	32 (100.0)
5–8 years	23 (42.6)	23 (42.6)	8 (14.8)	54 (100.0)	27 (50.0)	25 (46.3)	2 (3.7)	54 (100.0)
>8 years	9 (75.0)	2 (16.7)	1 (8.3)	12 (100.0)	11 (91.7)	1 (8.3)	0 (0.0)	12 (100.0)
Total	41 (36.0)	55 (48.2)	18 (15.8)	114 (100.0)	54 (46.5)	52 (45.6)	8 (7.0)	114 (100.0)

improved significantly after treatment with either ALR or ST (Table 3). Other improvements in study subjects' behavior were also recorded after treatment (Table 3).

The results showed that the mean AHI was significantly reduced in comparison with before treatment in study subjects treated with ALR (0.9 ± 1.0 vs. 3.9 ± 2.7 events/h; $p = 0.001$; Table 3) or with ST (3.5 ± 1.4 vs. 23.4 ± 13.1 events/h; $p < 0.001$; Table 3). Nadir SpO2 was significantly improved in study subjects treated with ALR or ST (83.7 ± 11.8 vs. 78.8 ± 11.9% and 81.4 ± 11.3 vs. 71.9 ± 14.9%; $p = 0.16$ and $p = 0.002$; respectively; Table 3). Snoring events were also reduced with LTR treatment or ST vs. before in all study subjects (154.8 ± 104.2 vs. 276.6 ± 257.3 events/h and 221.3 ± 256.4 vs. 663.6 ± 433.2 events/h; $p = 0.120$ and $p = 0.080$; respectively; Table 3). The percentage of study subjects without OSA was significantly increased after being treated with ALR or ST (47.6 vs. 0.0% and 3.9 vs. 0.0%; Figure 3). The percentage of study subjects with moderate OSA treated with ALR was significantly reduced (1.6 vs. 25.4%; Figure 3). The percentage of study subjects with severe OSA was clearly reduced after being treated with ST (7.9 vs. 86.2%; Figure 3).

Discussion

In the present study, OSA happened mainly in children from 5 to 8 years old and predominantly in boy (Tables 1A,B). Previous studies in both adults and children demonstrated that the prevalence of OSA in men is higher than women; and it might due to the respiratory tract of men are longer than women and more soft structure distribution in the upper respiratory tract (4). Although the percentage of children with low weight is low, there is only few children with overweight or obesity

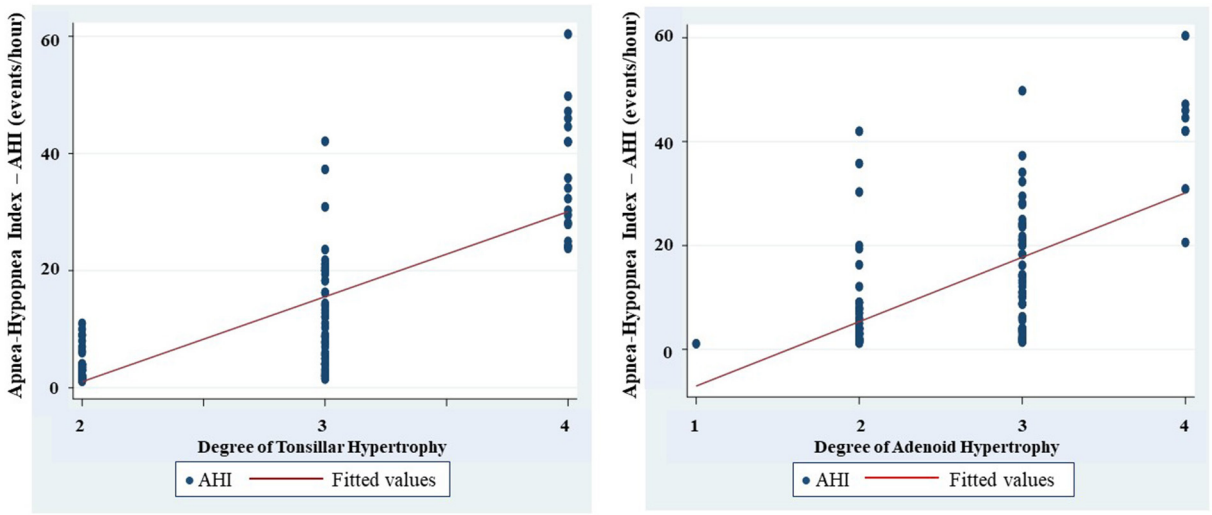

FIGURE 2
Correlation between degree of tonsilar and adenoid hypertrophy and apnea-hypopnea index (AHI).

TABLE 2 Anthropometric and respiratory polygraphy characteristics of study subjects classified by treatments.

Parameters	Total study subjects ($n = 114$)	Subjects treated with ST ($n = 51$)	Subjects treated with ALR ($n = 63$)	p^*
Anthropometry				
Age	5.5 ± 2.1	4.9 ± 1.9	5.9 ± 2.1	0.004
BMI	16.9 ± 3.2	17.7 ± 3.6	16.4 ± 2.8	0.030
Gender	-	-	-	-
Male, %	75.4	82.4	69.8	0.063
Female, %	24.6	17.6	30.2	0.123
Respiratory polygraphy				
AHI (event/h), mean ± SD	12.6 ± 11.2	23.4 ± 13.1	3.9 ± 2.7	<0.001
Mild, *N* (%)	48 (42.1)	1 (2.0)	47 (74.6)	<0.001
Moderate, *N* (%)	22 (19.3)	6 (11.8)	16 (25.4)	<0.001
Severe, *N* (%)	44 (38.6)	44 (86.2)	0 (0.0)	<0.001
SpO2, mean ± SD (%)	95.2 ± 5.6	94.0 ± 7.7	96.3 ± 2.4	0.008
SpO2 in the OSA period, mean ± SD (%)	80.6 ± 12.8	74.2 ± 13.9	86.0 ± 8.8	0.001
Nadir SpO2, mean ± SD (%)	75.7 ± 13.7	71.9 ± 14.9	78.8 ± 11.9	0.012
Average pulse, mean ± SD (%) (p/m)	87.7 ± 16.5	93.8 ± 18.7	82.7 ± 12.6	0.001
Snoring, mean ± SD (%) (event)	426.3 ± 315.9	633.6 ± 433.2	276.6 ± 257.3	0.054

BMI, body mass index; AHI, apnea-hypopnea index; SG, surgical therapy; ALR, anti-leukotriene receptor. *Subjects with ALR vs. SG.

(Table 1). This result is similar with other studies in Asia and different with those done in Western countries where high BMI increases the prevalence of OSA (19, 22, 23). In the present study, there is nearly all children had snoring at night (Table 1). This symptoms might be related to upper airway obstruction caused by tonsillar and/or adenoid hypertrophy. Obviously, the adeno-tonsillar hypertrophy was found mainly in children from 3 to 8 years old with the high rate in the present study (Table 1A). It is similar to the results of other authors and suggest that the main risk for the development of OSAS in young children is hypertrophy of tonsil and adenoid (12, 14).

It is clear that in the present study, the diagnosis of OSA is based on AHI measured by respiratory polygraphy as recommended by guidelines (5, 18, 24). AHI has been defined as

TABLE 3 Modification of clinical symptoms and respiratory polygraphy after treatment.

Symptoms	Study subjects treated with ALR ($n = 63$)						Study subjects treated with ST ($n = 51$)					
	Pre		Post		Δ	p^*	Pre		Post		Δ	p^*
	$\bar{X}$	SD	$\bar{X}$	SD			$\bar{X}$	SD	$\bar{X}$	SD		
Symptoms at night												
Snoring	3.1	0.4	1.2	0.4	1.87	<0.001	3.6	0.5	1.0	0.5	2.59	0.001
Snoring loudly	2.2	0.9	0.7	0.6	1.59		3.3	0.6	0.6	0.5	2.72	
Struggle to breath	1.9	0.8	0.3	0.2	1.68		2.8	0.9	0.4	0.3	2.39	
Sleep with opening mouth	2.2	0.7	0.7	0.5	1.48		3.3	0.5	0.5	0.4	2.9	
Stop breathing during sleep	0.6	0.4	0.1	0.3	0.52		2.4	1.0	0.3	0.2	2.18	
Congested nose at night	2.1	0.8	0.7	0.5	1.38		3.2	0.7	0.4	0.3	2.75	
Daytime symptoms												
Tend to breath by mouth during the day	1.2	0.8	0.3	0.2	0.89	0.001	2.5	1.1	0.4	0.3	2.14	0.001
Daytime sleepiness	0.7	0.2	0.4	0.3	0.26	0.03	1.6	1.3	0.8	0.6	0.78	0.001
Difficulty for sustaining attention in tasks	1.7	0.9	1.3	0.7	0.43	0.001	2.3	0.9	1.8	0.5	0.48	0.001
Fail of attention to details	1.8	0.8	1.3	0.7	0.46		2.3	0.8	1.8	0.5	0.51	
Lost of things (toy, pencil...)	1.5	1.3	1.2	1.1	0.31		2.7	1.1	1.9	0.8	0.8	
Easily distracted by extraneous stimuli	1.6	0.9	1.3	0.9	0.29		2.5	0.9	1.8	0.7	0.67	
Behavior												
Fidgets with hands or fiting on seat	1.2	1.1	0.9	0.8	0.32	0.001	2.2	1.1	1.5	0.9	0.75	0.001
Leaving seat in classroom	1.0	1.9	0.7	0.7	0.28	0.001	1.9	1.0	1.4	0.8	0.5	0.001
Answersing before question completed	0.9	0.5	0.8	0.7	0.11	0.220	1.5	0.9	1.2	0.9	0.22	0.002
Interrupting or intruding on others	1.4	1.2	1.1	0.9	0.32	0.001	2.0	0.9	1.7	0.8	0.31	0.001
Respiratory polygraphy												
AHI, mean ± SD (events/h)	3.9	2.7	0.9	1.0	3.0	0.001	23.4	13.1	3.5	1.4	19.8	<0.001
SpO2, mean ± SD (%)	96.3	2.4	95.5	4.8	0.8	0.244	94.0	7.7	95.2	3.6	1.2	0.060
SpO2 in OSA periode, mean ± SD (%)	86.0	8.8	88.4	7.8	2.6	0.099	74.2	13.9	86.3	9.4	12.1	0.001
Nadir SpO2, mean ± SD (%)	78.8	11.9	83.7	11.8	4.9	0.016	71.9	14.9	81.4	11.3	9.5	0.002
Minimum pulse, mean ± SD (p/min)	56.3	9.6	63.9	23.5	−7.6	0.001	62.6	24.5	62.1	29.0	0.5	0.230
Maximum Pulse, mean ± SD (p/min)	138.5	38.7	121.7	30.8	16.8	0.340	145.8	31.3	125.5	36.3	20.3	0.050
Average pulse, mean ± SD (p/min)	82.8	12.6	70.5	26.2	12.3	0.070	93.8	18.7	89.9	23.5	23.8	0.010
Snoring, mean ± SD (events)	276.6	257.3	154.8	104.2	121.8	0.120	663.6	433.2	221.3	256.4	412.3	0.080

ALR, anti-leukotriene receptor; SG, surgical therapy. *Post vs. pre treatment.

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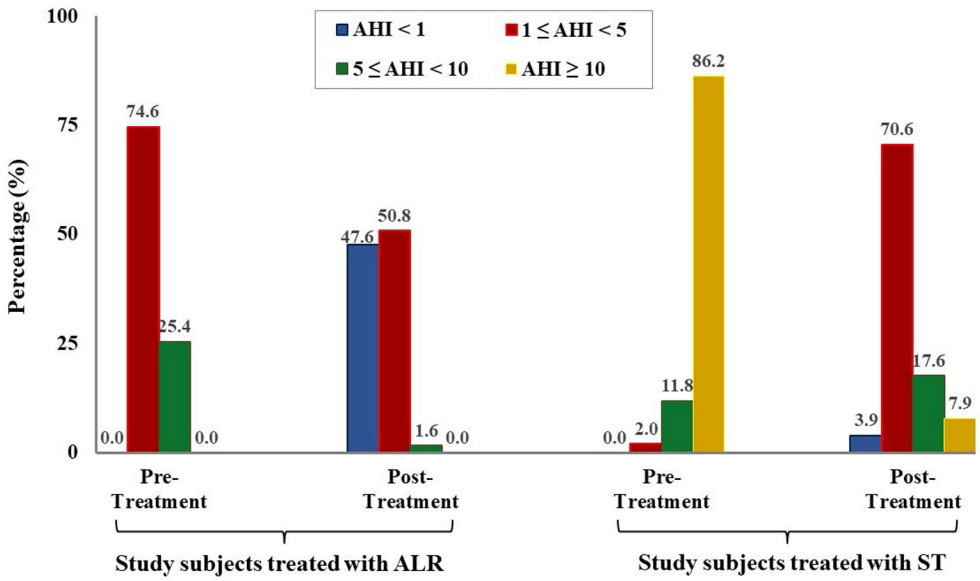

FIGURE 3
Modification of OSA severity after treatment in study subjects. AHI, apnea-hypopnea index; ALR, anti-leukotriene receptor; SG, surgical therapy.

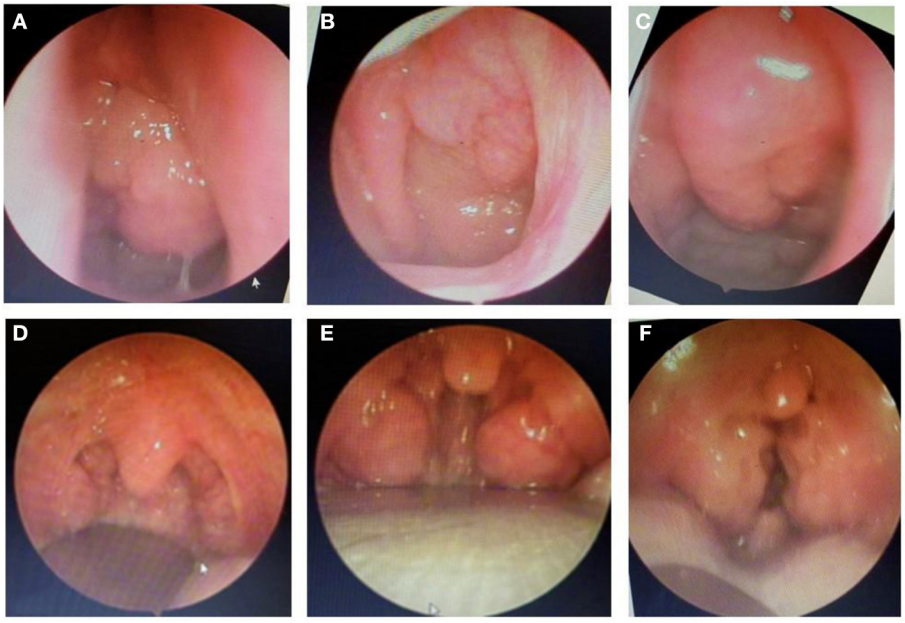

FIGURE 4
Endoscopic images of adenoid hypertrophy **(A–C)** and tonsillar hypertrophy **(D–F)**.

the total number of apnea and hypopnea divided by the number of sleeping hours. In children, the cut-off of AHI from 1–5, 5–10 and >10 has been used to refer to mild, moderate, and severe OSA respectively (25). This cut-off is much lower than those in adults (from 5–15, 15–30 and >30). Previous studies demonstrated that children are not mini-adults because many of their physical development processes happening during sleep (18, 24). Therefore, OSA leads to the differences in symptoms, influences and decisions on treatment options between children and adults (12, 14, 24, 25). In the present study, the mean AHI

of study subjects is 12.6 ± 11.2 events/ hour and considered as severe OSA. Although, OSA has been well developed in Vietnam in the last 10 years, the early detection of OSA is still difficult, particularly in children. In addition, the costs of respiratory polygraphy or polysomnography are still high and the techniques are time consuming in comparing with other diagnostic tests.

Interestingly, the present study found that there is a significant correlation between the hypertrophy of tonsils and adenoid with the severity of OSA measured by AHI (Figure 2). This result is similar to that reported from other authors (18, 25). Li et al. conducted a study on 1150 children and found that the size of the tonsils was an independent risk factor of OSA (26). The size of the tonsils increased by 25–50% could increase the risk of OSA by two times (OR = 2.0 and $p = 0.036$), the size of the tonsil increased 50–75% could increase the risk of OSA by five times (OR = 5.0 and $p = 0.022$), and if it increased by 75–100%, induced the risk of OSA by eight times (OR = 8.1 and $p < 0.001$).

Beside of that, different studies using universal snoring tools (scales or machines), also revealed the positive correlations between snoring severity (frequency, duration, time, or intensity) and AHI; it was also consistent with the results of present study (data not shown). Moreover, when studying the correlation between nadir SpO_2 and AHI, the present study found out a significant correlation between two parameters: the more severe of AHI level, the lower level of nadir SpO_2 (data not shown).

Obviously, the present study shows that the prominent symptoms of OSA were significantly reduced after treatment with ALR and surgical therapy (Table 3). Curiously, in children treated with ALR, the maximum pre- and post-treatment differences (Δmax) of symptoms in the attention deficit and hyperactivity symptom groups (Δmax) were lower than Δmax in the nighttime symptom and daytime symptom groups (Table 3). It might be explained by the apparent improvement in the daytime and nighttime symptom groups related to the fact that ALR reduced the size of tonsil and adenoid hypertrophy and thereby reducing the narrowing of the upper respiratory tract (16, 17). However, in the present study, one children with mild OSA had ST due to increasing symptoms after ALR therapy (Table 2). Among clinical symptoms, morning headache was almost unchanged before and after treatment. This symptom is not common in study children of the present study because there was only 4.8% of them had morning headache (data not shown). But this symptom is quite common in adults with OSA which has been reported by other studies (27, 28). In the present study, children with OSA treated with surgery therapy (adeno-tonsillectomy) also improved significantly their symptoms related to OSA at night and during the day. The largest Δmax was found in symptoms at night and daytime groups while it was lowest for those with attention-reduction and hyperactivity groups (Table 3). Especially, all children with OSA did not have any comorbidities or other current treatments. This result wass similar to previous published reports (12, 25).

Finally, the present study demonstrated that after treatment with ALR or ST, the severity of OSA was significantly reduced in study subjects. It is clear that the percentage of children with moderate or severe OSA was reduced by treated with ALR or ST and the mean SpO2 and nadir SpO2 was significantly improved after treatment (Figure 3 and Table 3). These results were similar to previous studies (12, 16, 17, 25). In the present study, surgery therapy seems to be the best effective treatment for children with adenotonsillar hypertrophy associated with or without adenoid hypertrophy (illustrated images from study patients presented in Figure 4) having severe OSA because it improved significantly AHI index and reduced the percentage of severe OSA after interventional procedure (Figure 3). Other works reported the successful rate of treatment for OSA in children with adenotonsillar hypertrophy by surgery method are also very different and depended on centers. The reported successfull rates range from 24 to 100% depending on the study criteria.

Finally, the present study showed that after 12 weeks of ALR treatment, there was no case with side effects requiring discontinuation. Hence, this treatment could be an effective therapy for improving both clinical symptoms and respiratory polygraphy. This medical treatment option might be used as an alternative choice of surgery for adenotonsillar hypertrophy. For study children who underwent adenotonsillar hypertrophy surgery, there was only <10% of reported cases with controlled bleeding during or after the first week of surgery. The main limitation of the present study is related to the short duration of patients' follow-up (three months) with the use of PSQ questionnaires was only 3 months after treatment. Therefore, the long-term follow-up could be necessary for evaluating the significant improvement of recurrent clinical symptoms and hyperactivity and attention deficit in children with OSA.

Conclusion

OSA is common in children with adenotonsillar hypertrophy. Children with OSA usually have the symptoms at night and its consequences during the day. The severity of adeno-tonsillar hypertrophy is correlated with the severity of OSA measured by apnea-hypopnea index. Fortunately, the treatment of OSA due to adeno-tonsillar hypertrophy with ALR for moderate OSA or surgery for severe OSA can improve children health by reducing nightime and daytime symptoms. However, more studies with long-term follow-up are necessary to evaluate the improvement other daytime consequences of OSA in children with adeno-tonsillar hypertrophy, especially those related to attention decifit and hyperactivity disorders.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of Hanoi Medical University and National Pediatric Hospital (No. 99/HDDD-DHYHN). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

DT-M, AP-T-Q, PN-D, and SD-Q: conceptualization, methodology, formal analysis, writing–original draft preparation, and writing–review and editing. DT-M, AP-T-Q, and PN-D: software and validation. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Relationship between sleep disorders and the prognosis of neurological function after stroke

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Objective: This study aims to investigate the effects of sleep disorders on the prognosis of neurological function after stroke and other factors affecting the prognosis after stroke.

Method: We designed a cohort study. A total of 1,542 patients with their first stroke were hospitalized in the department of neurology of Tianjin Huanhu Hospital from 2015.6.1 to 2016.12.31. We recorded the personal histories of patients. The MMSE (mini-mental state examination), MoCA (Montreal Cognitive Assessment), HAMD (Hamilton Depression Scale), National Institutes of Health Stroke Scale (NIHSS) score, mRS (Modified Rankin Scale), BI (Barthel Index), PSQI (Pittsburgh Sleep Quality Index), ESS (Epworth Sleepiness Scale), Berlin questionnaire, and nocturnal TST (Total sleep time) were assessed before discharge, 3 months, 6 months, and 4 years (2019–2020) after stroke.

Result: Low sleep quality (OR 2.019, 95%CI 1.199–3.398, $p = 0.008$), nocturnal TST (<7 h) (OR 4.060, 95%CI 1.494–11.034, $p = 0.006$), nocturnal TST (>8 h) (OR 5.928, 95% CI 2.134–16.464, $p = 0.001$) were risk factors for poor neurological function recovery at 3 months after stroke. Nocturnal TST (<7 h) (OR 13.042, 95%-CI 2.576–66.027, $p = 0.002$) and nocturnal TST (>8 h) (OR 11.559, 95%-CI 2.108–63.390, $p = 0.005$) were risk factors for poor neurological function at 6 months after stroke. Nocturnal TST (<7 h) (OR 2.668, 95% CI 1.250–5.698, $p = 0.011$) and nocturnal TST (>8 h) (OR 2.516, 95% CI 1.080–5.861, $p = 0.033$) were risk factors for poor neurological function at 4 years after stroke. High risk of OSA (HR 1.582, 95%CI 1.244–2.012, $p < 0.001$) was a risk factor for all-cause death in patients followed up for 4 years after stroke.

Conclusion: Low sleep quality is associated with short-term poor neurological function after stroke. Unusual nocturnal TST (long or short) is associated with short-term or long-term poor neurological function after stroke. A high risk of OSA is associated with a higher risk of all-cause death after stroke.

KEYWORDS

sleep disorders, neurological function, nocturnal total sleep time, sleepiness, OSA

Introduction

Stroke is a common cerebrovascular disease. Approximately 16 million people worldwide experience their first stroke each year, of which ∼5.7 million die, and another approximately five million people are left with a disability. Stroke is the third leading cause of death in men after heart disease and lung cancer, and the second leading cause of death in women (1).

Stroke is one of the leading causes of disability. Neurological function after stroke varies greatly in different individuals. The recurrence rate of stroke within 5 years is up to 17% (2). Thrombolytic drugs and endovascular therapy have revolutionized the status of acute stroke patients. However, for the vast majority of patients who remain disabled after treatment, there are significant challenges in improving neurological recovery and preventing stroke recurrence.

Stroke is the leading cause of death in China, accounting for 20% of all deaths every year. Understanding the risk factors for stroke is essential for better treatment. Hypertension, diabetes, atrial fibrillation, obesity, and smoking have been shown to be risk factors for stroke. The number of stroke patients, morbidity, mortality, and the associated social burden are high and increasing in China. The high burden of a stroke may be explained by the less significant changes in traditional risk factors and the persistent influence of the less recognized risk factors (3). However, there are few domestic studies on the relationship between sleep disorders and stroke. Screening for post-stroke sleep disorders has not yet become part of the standard of routine care, and screening coverage is low.

Sleep disorders after stroke are common, and about 20–78% of patients have sleep disorders (4). The role of sleep disorders in stroke outcomes has become a thorny problem. Sleep disorders can cause intracranial cerebral atherosclerosis or small vessel diseases (5–8).

Sleep disorders after stroke are underestimated and generally overlooked because of the lack of awareness of sleep disorders among stroke patients. Although polysomnography (PSG) is the gold standard for diagnosing or differentiating sleep disorders, PSG cannot be applied to all stroke patients due to its high cost and limited accessibility. Other tools are also needed to screen for sleep disorders, such as valid sleep questionnaires, such as the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Sleepiness Scale, and Berlin questionnaire.

The purpose of this cohort study was to investigate the influence of longitudinal changes on sleep disorders (including sleep quality, sleepiness, nocturnal TST (Total sleep time), and obstructive sleep apnea (OSA), as measured by sleep questionnaires on neurological function and all-cause death in patients with stroke. Other factors affecting the neurological function of patients after stroke were also analyzed.

Research object

A total of 1,542 patients with the first stroke, including cerebral infarction, TIA, and cerebral hemorrhage, were hospitalized in the department of neurology of Tianjin Huanhu Hospital from 2015.6.1 to 2016.12.31. (1) The inclusion criteria were as follows: ① the patients were all admitted 72 h after onset, and ② the diagnosis of ischemic stroke meets the diagnostic criteria of the 2014 Chinese Guidelines for diagnosis and treatment of acute ischemic stroke (9). The intracerebral hemorrhage diagnosis met the guidelines for the management of spontaneous intracerebral hemorrhage—a guideline for healthcare professionals from the American Heart Association/American Stroke Association (10). The diagnosis of TIA met the diagnostic criteria for definition and evaluation of transient ischemic attacks—a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease (11). ③ Patients who can provide written informed consent and are willing to follow the 4-year follow-up protocol. (2) The exclusion criteria were as follows: ① patients under 18 years of age; ② patients with obvious liver and kidney dysfunction, heart failure, severe infection, or malignant disease; ③ patients with a prior history of brain disease and cognitive impairment; ④ patients with specific genetic diseases; ⑤ patients with aphasia, apraxia, disturbance of consciousness, visual and hearing impairment, and other conditions that make it difficult to perform functional tests, as well as those who cannot accurately provide reliable information; and ⑥ patients with sleep disorders before stroke (we specifically excluded people with a previous diagnosis of OSA, heavy snoring, nocturnal TST <7 h and >8 h, and those who considered themselves to be extremely sleepy during the day).

Research method

All enrolled patients underwent a detailed medical history, prior history, and personal history, as well as a detailed neurological examination, MRI, transcranial doppler, cervical ultrasound, MRA, or CTA. All patients underwent an MRI examination. According to MRI results, the lesions of the patients were divided into a dominant hemisphere and non-dominant hemisphere; large lesions (lesions larger than 4 cm in diameter or involving more than two lobes of the brain are called large lesions), brainstem lesions (midbrain, pons, and medulla oblongata lesions) and lesions in key areas (hippocampus, cingulate gyrus, and angular gyrus in cortical areas, thalamus, fornix, and basal ganglia in subcortical areas); multiple infarcts and non-multiple infarcts; microbleeds, and

TABLE 1 Basic information of all patients.

Gender	Male	1,056 (68.5%)
	Female	486 (31.5%)
Age (year)		61.58 ± 10.71
Education	≤6 years	490 (31.8%)
	>6 years	1,052 (68.2%)
Stroke type	TIA	156 (10.1%)
	Cerebral infarction	1,275 (82.7%)
	Cerebral hemorrhage	111 (7.1%)
Hemisphere	Dominant hemisphere	763 (49.5%)
	Non-dominant hemisphere	779 (50.5%)
Lesion	Large lesion	77 (49.9%)
	Brain-stem lesion	291 (18.9%)
	Critical sites lesion	482 (31.3%)
	Other lesions	692 (44.9%)
Multiple	Yes	597 (38.7%)
	No	945 (61.3%)
Microbleeds	Yes	464 (30.1%)
	No	1,078 (69.9%)
MTA scores		2.59 ± 1.40
Fazekas scores		1.27 ± 0.952
ICA arteriostenosis	Yes	695 (45.1%)
	No	847 (54.9%)
MCA arteriostenosis	Yes	652 (42.3%)
	No	890 (57.7%)
ACA arteriostenosis	Yes	126 (8.2%)
	No	1,416 (91.8%)
VA arteriostenosis	Yes	415 (26.9%)
	No	1,127 (73.1%)
BA arteriostenosis	Yes	210 (13.6%)
	No	1,332 (86.4%)
Hypertension	Yes	1,128 (73.2%)
	No	414 (26.8%)
Coronary heart disease	Yes	334 (21.6%)
	No	1,208 (78.4%)
Diabetes	Yes	463 (30%)
	No	1,079 (70%)
Drinking	Yes	644 (41.8%)
	No	898 (58.2%)
Smoking	Yes	747 (48.4%)
	No	795 (51.6%)
Systolic pressure (mmHg)	151.74 ± 25.80	
Diastolic pressure (mmHg)	84.12 ± 13.88	
Heart rate	68.68 ± 12.28	
Hcy (umol/L)	17.79 ± 3.38	
FBG (mmol/L)	6.47 ± 2.83	
TG (mmol/L)	1.78 ± 1.15	
TC (mmol/L)	6.02 ± 2.77	
HDL (mmol/L)	1.02 ± 0.38	
LDL (mmol/L)	7.17 ± 2.02	
MoCA scores	18.04 ± 7.08	
Depression	Yes	251 (16.3%)
	No	1,291 (83.7%)
Sleep quality	Low	942 (61.1%)
	High	600 (38.9%)
Sleepiness	Yes	383 (24.8%)
	No	1,159 (75.2%)
Nocturnal TST	7–8 h	379 (24.6%)
	<7 h	914 (59.3%)
	>8 h	249 (16.2%)
OSA	High risk	1,343 (87.1%)
	low risk	199 (12.9)
Wake-up stroke	Yes	593 (38.4%)
	No	949 (61.6%)
END	Yes	331 (21.5%)
	No	1,211 (78.5%)

non-microbleeds. The medial temporal lobe atrophy rating scale (MTA) and the Fazekas scale were performed. The patients' arteries (internal carotid artery, middle cerebral artery, anterior cerebral artery, vertebral artery, and basilar artery) were divided into stenosis and non-stenosis based on vascular examination. Systolic blood pressure, diastolic blood pressure, and heart rate were recorded. Homocysteine (Hcy), fasting blood glucose (FBG), triglycerides (TG), cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were recorded. The educational level of the patients was recorded in detail. Patients with <6 years of education (illiterate and primary school) were in the low-level education group, and those with more than 6 years of education were in the high-level education group.

Patients were given the detailed mini-mental state examination (MMSE) score, Montreal Cognitive Assessment (MoCA) score, Hamilton Depression Scale (HADM) score, National Institutes of Health Stroke Scale (NIHSS) score, Modified Rankin Scale (mRS) score, Barthel Index (BI), Pittsburgh Sleep Quality Index (PSQI) score, Epworth Sleepiness Scale (ESS) score, Berlin Questionnaire (BQ), and nocturnal total sleep time (TST) before discharge. The basic information of all patients was in Table 1. All patients were followed up at 3 months, 6 months, and 4 years (2019–2020) after stroke. During the follow-up, the above scores and questionnaires were conducted again to assess the relationship between the recovery of neurological function and the sleep status of the patients at that time. The endpoint was the end of follow-up, and the secondary endpoint was death. The flow chart of the research method was shown in Figure 1. The time

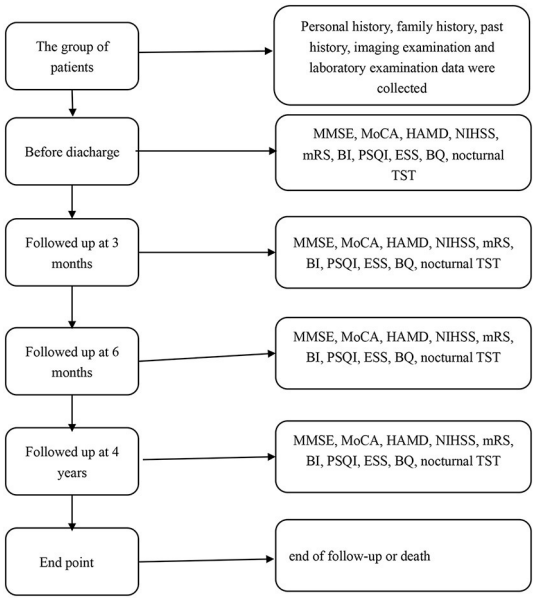

FIGURE 1
The flow chart of the research method.

of death and cause of death were recorded according to the patient's death certificate or medical record. Whether the patient had a wake-up stroke or early neurological deterioration (END) was recorded during the hospitalization. END was defined as an increase of ≥1 point in NIHSS motor score or ≥2 points in the total score during the 1st week after admission (12).

A total of 1,542 stroke patients were enrolled, and 188 patients were lost to follow-up. Among the 188 patients, 56 went to other places and could not cooperate with the follow-up, 103 withdrew from the follow-up, and 29 patients could not be contacted because their contact information had changed. A total of 1,354 patients, including 144 who died, completed follow-up. The flow chart of patients was shown in Figure 2.

All data were collected by neurologists and nurses through standard face-to-face questionnaires. Before the follow-up, all the investigators were given special training. The training included the purpose of the study, questionnaire management methods, questionnaire testing methods, and research procedures. We had specialists train our investigators on the cognitive scale, the neurologic scale, the depression scale, and the sleep disorders scale. The training was conducted in strict accordance with uniform guidelines, test procedures, and scoring standards. We needed to unify the instructions and operation procedures of each scale. After the training, the training personnel carried out practical operation drills and relevant assessments. Only qualified personnel could carry out the study. The personnel who assessed the scales at admission, 3 months after stroke, 6 months after stroke, and 4 years after stroke were different. In addition to bedside screening tests, we needed to ensure that tests were optimized and that patients could be evaluated in a neuropsychological testing room with an appropriate testing environment that eliminates test anxiety and allows adequate time and rest. Investigators were given adequate guidance and assistance during data collection.

This study has been ethically approved by the Tianjin Huanhu Hospital. The purpose of the study had been explained to all participants, confidentiality had been promised, and participants had been informed of their right to withdraw.

Assessment of cognitive function

The Mini-mental State Scale (MMSE) and the Montreal Cognitive Assessment Scale (MoCA) are the most widely used cognitive function screening scales in a clinic. The MMSE, developed by Folstein in 1975, is one of the most widely used screening tools for cognitive impairment, and scores are easily influenced by education level. MMSE is poor at identifying early dementia, especially mild cognitive impairment. The MMSE consists of six aspects and a total of 30 questions. The Montreal Cognitive Assessment (MoCA) is a tool used to screen for cognitive impairment. The scale has been translated into many languages, and the popular versions in China are Beijing, Beijing-Guangzhou (Mandarin), Changsha, Cantonese, Hong Kong, and Taiwan. MoCA can detect the earliest stage of cognitive impairment. The MoCA measures eight cognitive domains: memory function, visuospatial function, executive function, attention, computation, language function, temporal orientation, and spatial orientation. The specificity of the Montreal Cognitive Scale (MoCA) for screening mild cognitive impairment (MCI) was 88.4%, and although it was slightly lower than the Mini-Mental State Examination (MMSE) (100%), its sensitivity to MCI was 92.4%, significantly better than that of the MMSE (24.2%). MoCA and MMSE can complement each other.

Assessment of neurological function

The National Institutes of Health Stroke Scales (NIHSS) is a comprehensive acute stroke scale that major hospitals have widely adopted in China. The NIHSS score has 42 points and 11 items. It considers the symptoms of the anterior and posterior circulation and is an objective semi-quantitative stroke severity evaluation tool. It has been widely used in several international multicenter randomized controlled studies and is a recognized scoring system for the severity stratification of stroke patients with good reproducibility.

The Barthel Index (BI) was published by Florence Mahoney and Dorothea Barthel in the United States in 1965. The BI has comprehensive content, clear scoring, simple operation, high sensitivity, and good reliability and validity in face-to-face and

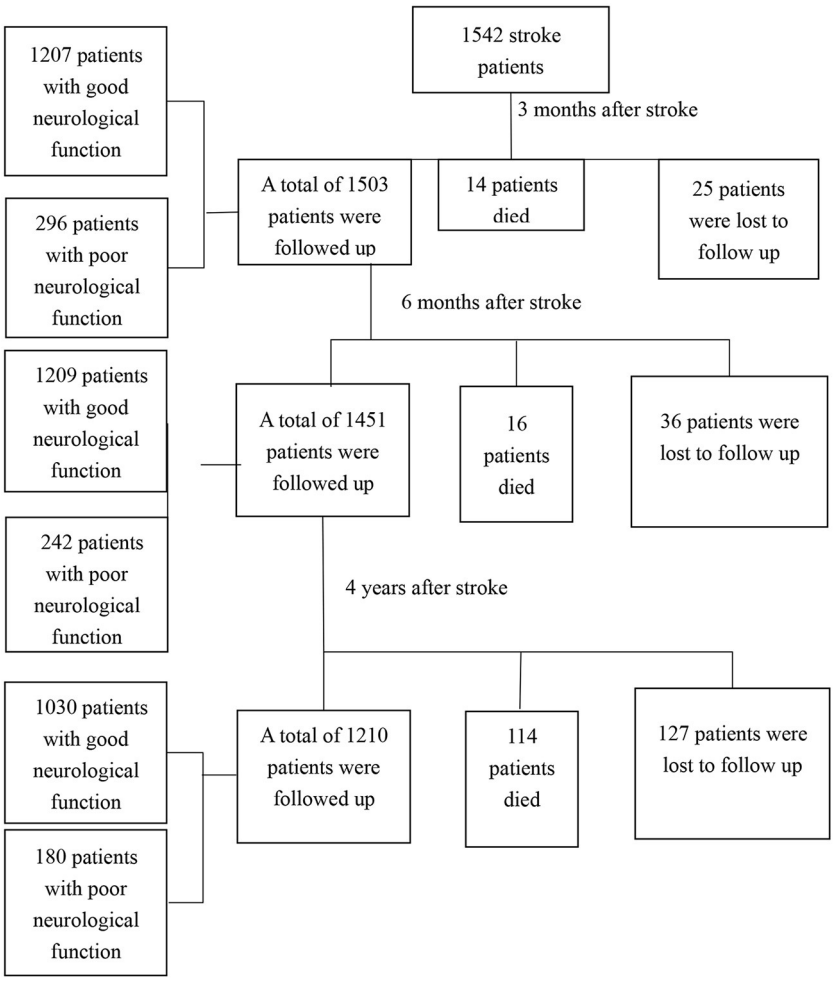

FIGURE 2
The flow chart of patients.

telephone evaluations. In clinical applications, BI is used to assess baseline disability, assist in rehabilitation planning, and quantify functional changes after rehabilitation. BI is widely used in stroke clinical trials as a functional outcome measure. The Barthel Index includes ten items, which are divided into four functional grades (0, 5, 10, and 15 points), depending on the need for help and the degree of help, with a total score of 100 points. The higher the score, the more independent and less dependent it is. The mRS score is used to measure the neurological recovery status of patients after a stroke. It assesses the ability to live independently, including physical function, mobility, and daily life participation. It is divided into five levels. mRS $\leq$2 indicated a good prognosis of neurological function, and mRS>2 indicated a poor prognosis of neurological function. mRS at 3 and 6 months after stroke represented short-term neurological outcomes, and mRS at 4 years after stroke represented long-term neurological outcomes.

Assessment of depression

Developed by Hamilton in 1960, the HAMD is the most commonly used self-measuring depression scale in the clinical evaluation of depression. The Hamilton Depression Scale (HAMD) has good reliability and validity. It can reflect the changes in depressive symptoms more sensitively and is considered one of the best evaluation tools in therapeutic research. The total score can better reflect the severity of depression; the milder the disease, the lower the total score. A total score of more than eight is considered depression.

Assessment of sleep disorder

PSQI was developed in 1989 by Dr. Buysse, a psychiatrist at the University of Pittsburgh. It was used to evaluate sleep quality

in clinical and basic research. Liu Xianchen translated the scale into Chinese in 1996 and conducted a study on its reliability and validity. The results showed that the scale also had high reliability and validity when applied to China. The PSQI is a self-reported questionnaire used to assess sleep quality. It contains 19 questions that indicate overall sleep quality. Each question is weighed into seven components on a 0–3 interval scale. PSQI <5 indicates high sleep quality, and PSQI ≥ 5 indicates low sleep quality.

BQ can be used to evaluate obstructive sleep apnea syndrome (OSAS) with a sensitivity of 60–70% and a specificity of 15–55% (13, 14).

BQ consists of ten questions divided into three categories: severity of snoring, excessive daytime sleepiness, and a history of hypertension or obesity. Patients with two or more positive categories were classified as "high-risk OSA patients," and patients with one category of positive or asymptomatic groups were classified as "low-risk OSA patients (15)."

The ESS scale is a subjective evaluation of excessive daytime sleepiness (EDS) designed by the Epworth Sleep Research Center in Australia and is widely used in various sleep centers. It is one of the most practical sleep scales recognized internationally because of its accurate judgment and strong family self-test. The total score of ESS is 0–24, and an overall score of ≥ 10 indicates daytime sleepiness.

Statistics

SPSS software (version 17.0) was used for data processing and analysis. Logistic univariate regression analysis was used to analyze the factors affecting the neurological function of patients at 3 months, 6 months, and 4 years after stroke. The dependent variable was neurological function, where mRS ≤ 2 was coded as 0, and mRS >2 was coded as 1. The significance of the univariate analysis and the factors associated with sleep disorders (sleep quality, sleepiness, nocturnal TST, and OSA) were included in the multivariate logistic regression analysis. The stepwise forward method was used to select the variables that were eventually included in the model. A survival analysis was performed for all patients who died during the 4-year follow-up. In the survival analysis, group data were presented as mean ± standard deviation for normal distributions and n (%) or median (interquartile range) for skewed distributions. Group comparisons were performed using the Student's *t*-test, variance analysis of variance, or chi-square test as appropriate. Sleep disorders at admission were used as co-variables in the all-cause death-survival analysis of patients who died. Death was a dependent variable. Death was coded as one. Among the co-variables, stroke was classified into TIA, cerebral hemorrhage, and cerebral infarction, with cerebral hemorrhage as the reference category. Nocturnal TST was divided into 7–8 h, <7 h, and >8 h, with 7–8 h as the reference category. The lesions were divided into the large brainstem, key sites, and other lesions; other lesions were used as references. A two-sided *P*-value <0.05 was considered statistically significant.

Results

Three months after stroke, there were 1,207 patients with good neurological function (mRS ≤ 2), 296 patients with poor neurological function (mRS >2), and 14 patients (0.7%) with death. Univariate and multivariate logistic analyses of neurological function 3 months after stroke were shown in Table 2 (mRS ≤ 2 was coded as 0, mRS $>$ two was coded as 1).

Univariate and multivariate logistic analyses of neurological function 3 months after stroke are shown in Table 2. Logistic univariate analysis showed gender, age, education, stroke type, dominant hemisphere, stroke lesion, multiple lesions, MTA score, Fazekas score, microbleeds, ICA stenosis, MCA stenosis, VA stenosis, BA stenosis, drinking, smoking, systolic blood pressure, heart rate, TG, MoCA scores, depression at 3 months, sleep quality, sleepiness, OSA, wake-up stroke, and END were statistically significant ($p < 0.05$). A multivariate logistic analysis of these factors was performed. In multivariate logistic analysis, large lesion (OR 3.992, 95% CI 1.754–9.083, $p = 0.001$), high Fazekas score (OR 1.506, 95% CI 1.266–1.790, $p < 0.001$), heart rate (OR 1.019, 95% CI 1.002–1.036, $p = 0.028$), low sleep quality (OR 2.019, 95% CI 1.199–3.398, $p = 0.008$), nocturnal TST (<7 h) (OR 4.060, 95% CI 1.494–11.034, $p = 0.006$), nocturnal TST (>8 h) (OR 5.928,95% CI 2.134–16.464, $p = 0.001$), wake-up stroke (OR 5.060, 95% CI 3.300–7.758, $p < 0.001$) were risk factors for poor neurological function recovery at 3 months after stroke. The neurological function recovery of TIA (OR 0.128, 95% CI 0.031–0.539, $p = 0.005$) and cerebral infarction (OR 0.097, 95% CI 0.040–0.237, $p < 0.001$) was better than that of intracerebral hemorrhage; thus, patients with intracerebral hemorrhage had poor neurological function.

6 months after the stroke, there were 1,209 patients with good neurological function, 242 patients with poor neurological function, and 16 patients who died. Univariate and multivariate logistic analyses of neurological function 6 months after stroke are shown in Table 3.

Logistic univariate analysis showed gender, age, education, stroke type, stroke lesion, multiple lesions, MTA score, Fazekas score, microbleeds, ICA stenosis, MCA stenosis, VA stenosis, BA stenosis, drinking, smoking, systolic blood pressure, heart rate, TG, the score of MoCA at 6 months after stroke, depression at 6 months, sleep quality, sleepiness, OSA, nocturnal TST, wake-up stroke, and END were statistically significant ($p < 0.05$). A multivariate logistic analysis of these factors was performed.

Logistic multivariate analysis showed that patients with TIA (OR 0.107, 95% CI 0.013–0.870, $p = 0.037$) and cerebral infarction (OR 0.104, 95%-CI 0.029–0.374, $p = 0.001$) had better neurological function than patients with cerebral hemorrhage at

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TABLE 2 Univariate and multivariate logistic analysis of neurological function three months after stroke.

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Population information	Gender (male)	0.554 (0.420–0.731)	<0.001*	NA	
	Age	1.038 (1.025–1.052)	<0.001*	NA	
	low level of education	1.507 (1.141–1.992)	<0.001*	NA	
Stroke type	TIA	0.235 (0.114–0.483)	<0.001*	0.128 (0.031–0.539)	0.005
	cerebral infarction	0.552 (0.347–0.876)	0.012*	0.097 (0.040–0.237)	<0.001
Lesion characteristics	dominant hemisphere	1.392 (1.056–1.835)	0.021*	NA	
	Large lesion	4.361 (2.517–7.556)	<0.001*	3.992 (1.754–9.083)	0.001
	brainstem lesion	1.171 (0.781–1.754)	0.445	NA	
	critical sites lesion	1.610 (1.160–2.235)	0.004*	NA	
	multiple lesions	2.590 (1.949–3.442)	<0.001*	NA	
	MTA score	2.097 (1.801–2.442)	<0.001*	NA	
	Fazekas score	1.723 (1.551–1.913)	<0.001*	1.506 (1.266–1.790)	<0.001
	Microbleeds	3.077 (2.330–4.063)	<0.001*	NA	
arteriostenosis	ICA	1.713 (1.301–2.255)	<0.001*	NA	
	MCA	1.564 (1.189–2.057)	0.002*	NA	
	ACA	1.188 (0.738–1.914)	0.948	NA	
	VA	1.485 (1.106–1.993)	0.015*	NA	
	BA	2.122 (1.492–3.019)	0.021*	NA	
Risk factors	Hypertension	1.254 (0.911–1.725)	0.241	NA	
	coronary heart disease	0.726 (0.514–1.026)	0.068	NA	
	Diabetes	0.968 (0.718–1.304)	0.936	NA	
	Drinking	0.668 (0.503–0.889)	0.007*	NA	
	Smoking	0.691 (0.524–0.911)	0.010*	NA	
Blood pressure and heart rate	systolic pressure	1.013 (1.007–1.018)	<0.001*	NA	
	diastolic pressure	1.001 (0.991–1.011)	0.809	NA	
	heart rate	1.014 (1.003–1.026)	0.016*	1.019 (1.002–1.036)	0.028
laboratory examination	Hcy	0.996(0.984–1.009)	0.533	NA	
	FBG	0.982 (0.932–1.034)	0.405	NA	
	TG	0.825 (0.704–0.967)	0.017*	NA	
	TC	0.999 (0.991–1.006)	0.730	NA	
	HDL	1.124 (0.796–1.588)	0.502	NA	
	LDL	0.993 (0.963–1.023)	0.442	NA	
Patients status at three months after stroke	MoCA scores	0.883 (0.864–0.903)	<0.001*	NA	
	Depression	4.610 (3.287–6.464)	<0.001*	NA	
	low sleep quality	3.531 (2.594–4.806)	<0.001*	2.019 (1.199–3.398)	0.008
	Sleepiness	1.788 (1.338–2.390)	<0.001*	NA	
	nocturnal TST (<7h)	0.040 (0.001–1.754)	0.095	4.060 (1.494–11.034)	0.006
	nocturnal TST (>8h)	0.036 (0.000–2.745)	0.132	5.928 (2.134–16.464)	0.001
	High risk OSA	2.644 (1.551–4.506)	<0.001*	NA	
Characteristics of cases	Wake–up stroke	2.577 (1.910–3.478)	<0.001*	5.060 (3.300–7.758)	<0.001
	END	8.523 (6.160–11.793)	<0.001*	NA	

*$p < 0.05$, items with statistical significance in univariate analysis were included in the multivariate logistic regression analysis.

TABLE 3 Univariate and multivariate logistic analysis of neurological function at six months after stroke.

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Population information	Gender (male)	0.542 (0.403–0.728)	<0.001*	NA	
	Age	2.718 (2.050–3.604)	<0.001*	NA	
	Low level of education	1.837 (1.367–2.468)	<0.001*	NA	
Stroke type	TIA	0.257 (0.115–0.573)	0.001*	0.107 (0.013–0.870)	0.037
	Cerebral infarction	0.654 (0.395–1.083)	0.099	0.104 (0.029–0.374)	0.001
Lesion characteristics	Dominant hemisphere	1.297 (0.965–1.743)	0.084	NA	
	Large lesion	3.300 (1.861–5.852)	<0.001*	NA	
	Brainstem lesion	1.113 (0.725–1.710)	0.624	NA	
	Critical sites lesion	1.471 (1.040–2.081)	0.029	NA	
	Multiple lesions	2.744 (2.025–3.717)	<0.001*	NA	
	MTA score	2.549 (2.150–3.022)	<0.001*	NA	
	Fazekas score	1.910 (1.700–2.145)	<0.001*	1.710 (1.320–2.215)	<0.001
	Microbleeds	3.479 (2.585–4.681)	<0.001*	NA	
Arteriostenosis	ICA	1.774 (1.319–2.386)	<0.001*	NA	
	MCA	1.624 (1.209–2.181)	0.002*	NA	
	ACA	1.375 (0.838–2.256)	0.300	NA	
	VA	1.558 (1.139–2.132)	0.008*	NA	
	BA	2.172 (1.498–3.149)	<0.001*	NA	
Risk factors	Hypertension	1.298 (0.917–1.838)	0.190	NA	
	Coronary heart disease	0.886 (0.620–1.265)	0.505	NA	
	Diabetes	1.021 (0.743–1.402)	0.899	NA	
	Drinking	0.652 (0.479–0.887)	0.008*	NA	
Blood pressure and heart rate	Smoking	0.693 (0.515–0.933)	0.017*	NA	
	Systolic pressure	1.015 (1.009–1.021)	<0.001*	NA	
	Diastolic pressure	0.998 (0.988–1.009	0.772	NA	
	Heart rate	1.014 (1.002–1.027)	0.023*	NA	
Laboratory examination	Hcy	0.999 (0.987–1.011)	0.844	NA	
	FBG	0.988 (0.935–1.044)	0.658	NA	
	TG	0.710 (0.583–0.865)	0.001*	NA	
	TC	0.999 (0.991–1.007)	0.768	NA	
	HDL	1.163 (0.817–1.656)	0.396	NA	
	LDL	0.992 (0.958–1.028)	0.486	NA	
Patients status at 6 months after stroke	MoCA score	0.862 (0.841–0.884)	<0.001*	NA	
	Depression	3.720 (2.639–5.243)	<0.001*	NA	
	low sleep quality	4.191 (3.036–5.786)	<0.001*	NA	
	Sleepiness	1.852 (1.192–2.877)	0.006*	NA	
	nocturnal TST (<7 h)	17.467 (8.499–35.897)	<0.001*	13.042 (2.576–66.027)	0.002
	nocturnal TST (>8 h)	15.913 (7.325–34.571)	<0.001*	11.559 (2.108–63.390)	0.005
	High risk OSA	3.459 (1.794–6.669)	<0.001*	NA	
Characteristics of cases	Wake–up stroke	2.913 (2.101–4.040)	<0.001*	NA	
	END	10.15 (7.156–14.422)	<0.001*	5.961 (3.213–11.061)	<0.001

*$p < 0.05$, items with statistical significance in univariate analysis were included in the multivariate logistic regression analysis.

6 months after stroke; High Fazekas score (OR 1.710, 95% CI1. 320–2.215, $p < 0.001$), nocturnal TST (<7 h) (OR 13.042, 95%-CI 2.576–66.027, $p = 0.002$), nocturnal TST (>8 h) (OR 11.559, 95%–CI 2.108–63.390, $p = 0.005$) and END (OR 5.961 95% CI 3.213–11.061, $p < 0.001$) were risk factors for poor neurological function at 6 months after stroke.

4 years after the stroke, there were 1,030 patients with good neurological function, 180 patients with poor neurological function, and 114 patients who died. Univariate and multivariate logistics of neurological function 4 years after stroke are shown in Table 4.

Logistic univariate analysis showed gender, age, education, stroke lesion, multiple lesions, MTA score, Fazekas score, microbleeds, ICA stenosis, MCA stenosis, BA stenosis, systolic blood pressure, heart rate, MoCA score, depression, sleep quality, sleepiness, OSA, nocturnal TST, wake-up stroke, and END were statistically significant ($p < 0.05$). A multivariate logistic analysis of these factors was performed.

Logistic multivariate analysis showed that MTA score (OR 1.649,95% CI 1.208–2.251, $p = 0.002$), Fazekas score (OR 1.323, 95% CI 1.068–1.639, $p = 0.01$), ICA arteriostenosis (OR 1.858,95% CI 1.195–2.889, $p = 0.006$), depression (OR 5.226, 95% CI 3.353–8.147, $p < 0.001$), nocturnal TST (<7 h) (OR 2.668, 95% CI 1.250–5.698, $p = 0.011$), nocturnal TST (>8 h) (OR 2.516,95% CI 1.080–5.861, $p = 0.033$), END (OR 5.226, 95% CI 3.353–8.147, $p < 0.001$) were risk factors for poor neurological function at 4 years after stroke.

At the end of the 4-year follow-up, of the 1,354 patients who completed the follow-up, 1 210 patients were still alive (89.4%), and 144 patients had died (10.6%). Basic information on dead patients and survivors 4 years after stroke is shown in Table 5. Univariate and multivariate COX analysis of the influencing factors of all-cause death is shown in Table 6 (survivors were coded 0, and dead patients were coded 1).

Univariate and multivariate COX analysis of the influencing factors of all-cause death (survivors were coded 0 and dead patients were coded 1) is shown in Table 6. Univariate COX analysis revealed age, education, multiple lesions, MTA score, Fazekas score, microbleeds, ICA stenosis, MCA stenosis, ACA stenosis, VA stenosis, BA stenosis, coronary heart disease, drinking, smoking, systolic blood pressure, diastolic blood pressure, MoCA score, NIHSS score, sleep quality, OSA, and nocturnal TST were statistically significant ($p < 0.05$). Multivariate COX analysis of these factors showed that ICA stenosis (HR 1.871, 95% CI 1.192–2.937, $p = 0.007$), BA stenosis (HR 1.725, 95% CI 1.095–2.717, $p = 0.019$), high risk of OSA (HR 1.582, 95% CI 1.244–2.012, $p < 0.001$) were risk factors for all-cause death in patients followed up for 4 years after stroke.

Discussion

Our study found that low sleep quality was a risk factor for poor neurological function 3 months after stroke. However, there was no significant effect on long-term neurological recovery after stroke. This study used a PSQI questionnaire to assess sleep quality. In clinical work, the PSQI questionnaire is a simple and effective method to assess sleep quality. Insomnia is associated with an increased incidence of stroke and a poor prognosis. A Taiwan study of 21,438 patients with insomnia and 64,314 age - and gender-matched patients without insomnia observed a 54% increased risk of stroke in patients with insomnia over a 4-year follow-up (16). There are limited data on the relationship between neurological function recovery after stroke and the effect of sleep quality, especially from large prospective cohort studies. One study found that a lower sleep score (poor sleep profile) using PSQI is associated with a higher risk of coronary heart disease (17). One study showed that post-stroke sleep disturbance is associated with poorer outcomes from strokes (18).

Our study found that nocturnal TST (<7 h) and nocturnal TST (>8 h) were risk factors for short-term or long-term poor neurological function after stroke. A study of 123 inpatient rehabilitations found that, after adjusting for confounding factors, insomnia was associated with reduced ability to do daily living and poor recovery (19). Sleep disorders can negatively affect health in several ways, but not directly. Laboratory studies have shown that short sleep duration disrupts glucose metabolism, which increases the risk of diabetes (20). Short sleep increases blood pressure, C-reactive protein, cortisol levels, and sympathetic nervous system activity, which can lead to hypertension and cerebrovascular disease. Studies have observed a J-shaped association between sleep duration and stroke, and people with a sleep duration of 7 h have the lowest risk of stroke (21). People who sleep longer have a higher risk of stroke than people who sleep shorter, and the risk of stroke increases by 13% for each 1-h increase in sleep time over 7 h (21). One study found that nocturnal TST of 7–8 h can reduce the risk of stroke, and nocturnal TST ≥9 h is associated with an increased risk of stroke in 45–65-year-old people (22). Studies have shown a "U" type relationship between TST and stroke (23). Long nocturnal TST is a potential risk factor for stroke, which may be related to sympathetic activation. Long nocturnal TST increases the activity of orexin and inflammatory response, leading to elevated lipid levels and an increased risk of stroke. The increase in sleep time may be due to an initial lack of sleep, followed by more sleep to compensate for the previous lack of sleep. However, "lie-in" cannot alleviate the metabolic disorders caused by insufficient sleep and may even aggravate

TABLE 4 Univariate and multivariate logistic of neurological function at 4 years after stroke.

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Population information	Gender (male)	0.590 (0.426–0.818)	0.002*	NA	
	Age	1.049 (1.032–1.066)	<0.001*	NA	
	Low level of education	1.812 (1.309–2.508)	<0.001*	NA	
Stroke type	TIA	0.424 (0.148–1.215)	0.110	NA	
	Cerebral infarction	1.503 (0.762–2.967)	0.240	NA	
Lesion characteristics	Dominant hemisphere	1.315 (0.952–1.817)	0.097	NA	
	Large lesion	2.7561.452–5.230)	0.002*	NA	
	Brainstem lesion	0.954 (0.595–1.528)	0.844	NA	
	Critical sites lesion	1.335 (0.919–1.938)	0.129	NA	
	Multiple lesions	2.793 (2.012–3.877)	<0.001*	NA	
	MTA score	2.842 (2.336–3.457)	<0.001*	1.649 (1.208–2.251)	0.002
	Fazekas score	2.076 (1.816–2.374)	<0.001*	1.323 (1.068–1.639)	0.010
	Microbleeds	5.349 (3.829–7.473)	<0.001*	NA	
Arteriostenosis	ICA	1.649 (1.191–2.282)	0.002*	1.858 (1.195–2.889)	0.006
	MCA	1.397 (1.009–1.934)	0.043*	NA	
	ACA	1.345 (0.761–2.376)	0.307	NA	
	VA	1.411 (0.991–2.008)	0.056	NA	
	BA	2.269 (1.491–3.455)	<0.001*	NA	
Risk factors	Hypertension	1.263 (0.864–1.846)	0.939	NA	
	Coronary heart disease	0.673 (0.435–1.041)	0.075	NA	
	Diabetes	1.006 (0.708–1.430)	0.604	NA	
	Drinking	0.721 (0.516–1.005)	0.556	NA	
Blood pressure and heart rate	Smoking	0.832 (0.602–1.151)	0.623	NA	
	Systolic pressure	1.014 (1.008–1.020)	<0.001*	NA	
	Diastolic pressure	0.999 (0.988–1.011)	0.899	NA	
	Heart rate	1.015 (1.001–1.029)	0.031*	NA	
Laboratory examination	Hcy	0.989 (0.970–1.008)	0.233	NA	
	FBG	0.995 (0.938–1.056)	0.868	NA	
	TG	0.888 (0.751–1.051)	0.168	NA	
	TC	0.984 (0.853–1.136)	0.552	NA	
	HDL	0.909 (0.559–1.480)	0.702	NA	
	LDL	0.872 (0.713–1.066)	0.492	NA	
Patients status at 4 years after stroke	MoCA score	0.821 (0.797–0.846)	<0.001*	NA	
	Depression	4.535 (3.260–6.308)	<0.001*	5.226 (3.353–8.147)	<0.001
	Low sleep quality	3.633 (2.572–5.133)	<0.001*	NA	
	Sleepiness	2.600 (1.865–3.626)	0.006*	NA	
	Nocturnal TST (<7 h)	10.133 (5.530–18.568)	<0.001*	2.668 (1.250–5.698)	0.011
	Nocturnal TST (>8 h)	10.412 (5.287–20.502)	<0.001*	2.516 (1.080–5.861)	0.033
	High risk OSA	2.355 (1.278–4.338)	0.006*	NA	
Characteristics of cases	Wake–up stroke	3.001 (2.166–4.158)	<0.001*	NA	
	END	10.628 (7.485–15.090)	<0.001*	5.226 (3.353–8.147)	<0.001

*$p < 0.05$, items with statistical significance in univariate analysis were included in the multivariate logistic regression analysis.

TABLE 5 Basic information of dead patients and survivors 4 years after stroke.

		Survivors	Died patients	t/χ^2	p
Gender	Male	837 (69.2%)	90 (62.5%)	2.654	0.103
	Female	373 (30.8%)	54 (37.5%)		
Age (year)		60.45 ± 10.33	70.62 ± 9.49	−11.394	<0.001
Education	≤6 years	370(30.6%)	58(40.3%)	5.600	0.018
	>6 years	840(69.4%)	86 (59.7%)		
Stroke type	TIA	121 (10.0%)	18 (12.5%)	0.919	0.632
	Cerebral infarction	1,000 (82.6%)	115 (79.9%)		
	Cerebral hemorrhage	89 (7.4%)	11 (7.6%)		
Hemisphere	Dominant hemisphere	567 (50.2%)	61 (44.2%)	1.756	0.185
	Non-dominant hemisphere	563 (49.8%)	77 (55.8%)		
Lesion	Large lesion	78 (6.4%)	13 (9.0%)	1.594	0.661
	Brain-stem lesion	234 (19.3%)	29 (20.1%)		
	Critical sites lesion	374 (30.9%)	41 (28.5%)		
	Other lesions	524 (43.3%)	61 (42.4%)		
Multiple	Yes	422 (37.9%)	68 (47.2%)	4.607	0.032
	No	690 (62.1%)	76 (52.8%)		
Microbleeds	Yes	331 (27.4%)	76 (52.8%)	39.560	<0.001
	No	879 (72.6%)	68 (47.2%)		
MTA scores		1.19 ± 0.92	1.96 ± 0.93	−9.642	<0.001
Fazekas scores		2.49 ± 1.38	3.42 ±1.32	−7.751	<0.001
ICA arteriostenosis	Yes	527 (43.6%)	82 (56.9%)	9.324	0.002
	No	683 (56.4%)	62 (43.1%)		
MCA arteriostenosis	Yes	504 (41.7%)	74 (52.3%)	4.986	0.026
	No	706 (58.3%)	70 (47.7%)		
ACA arteriostenosis	Yes	115 (9.5%)	18 (12.5%)	1.304	0.254
	No	1,095 (90.5%)	126 (87.5%)		
VA arteriostenosis	Yes	317 (26.2%)	60 (41.7%)	15.326	<0.001
	No	893 (73.8%)	84 (58.3%)		
BA arteriostenosis	Yes	167 (13.8%)	40 (27.8%)	19.409	<0.001
	No	1,043 (86.2%)	104 (72.2%)		
Hpertension	Yes	882 (72.9%)	102 (70.8%)	0.275	0.600
	No	328 (27.1%)	42 (29.2%)		
Coronary heart disease	Yes	243 (20.1%)	52 (36.1%)	19.401	<0.001
	No	967 (79.9%)	92 (63.9%)		
Diabetes	Yes	366 (30.2%)	46 (31.9%)	0.175	0.676
	No	844 (69.8%)	98 (68.1%)		
Drinking	Yes	536 (44.3%)	34 (23.6%)	22.592	<0.001
	No	674 (55.7%)	110 (76.4%)		
Smoking	Yes	612 (50.6%)	46 (31.9%)	17.887	<0.001
	No	598 (49.4%)	98 (68.1%)		
systolic pressure (mmHg)		150.97 ± 25.90	157.77 ± 24.55	−3.008	0.003
Diastolic pressure (mmHg)		84.53 ± 14.09	80.79 ± 11.77	3.534	0.001
Heart rate		68.70 ± 12.35	70.00 ± 11.77	−1.189	0.234
Hcy (umol/L)		18.31 ± 20.25	14.13 ± 9.34	1.579	0.115
FBG (mmol/L)		6.45 ± 2.82	6.72 ± 2.91	−1.054	0.292

(Continued)

TABLE 5 (Continued)

		Survivors	Died patients	t/χ^2	p
TG (mmol/L)		1.804 ± 1.18	1.61 ± 0.88	1.788	0.074
TC (mmol/L)		6.02 ± 26.24	5.99 ± 6.20	0.013	0.990
HDL (mmol/L)		1.01 ± 0.39	1.04 ± 0.29	−0.825	0.409
LDL (mmol/L)		7.65 ± 90.33	3.45 ± 0.87	0.541	0.589
MoCA scores		18.50 ± 6.93	14.43 ± 7.28	6.695	<0.001
Depression	Yes	192 (15.9%)	30 (20.8%)	2.315	0.128
	No	1,018 (84.1%)	114 (79.2%)		
Sleep quality	Low	719 (59.4%)	108 (75.0%)	13.137	<0.001
	High	491 (40.6%)	36 (25.0%)		
Sleepiness	Yes	294 (24.3%)	42 (29.2%)	1.635	0.201
	No	916 (75.7%)	102 (70.8%)		
Nocturnal TST	7–8 h	322(26.6%)	12(8.3%)	23.508	<0.001
	<7 h	694(57.4%)	106(73.6%)		
	>8 h	194(16.0%)	26(18.1%)		
OSA	High risk	1,031 (85.1%)	143 (99.3%)	22.458	<0.001
	low risk	181 (14.9%)	1 (0.7%)		
Wake-up stroke	Yes	511 (42.2%)	57 (39.6%)	0.371	0.543
	No	699 (57.8%)	87 (60.4%)		
END	Yes	263 (21.7%)	29 (20.1%)	0.194	0.660
	No	947 (78.3%)	115 (79.9%)		

the metabolic disorders (24). "Sleep deprivation" can have adverse effects, but "sleep compensation" does not ameliorate those effects. Prolonged sleep duration may be a sign of subclinical disease.

The EES scale is widely used in the field of sleep medicine as a subjective measure of sleepiness in patients. Sleepiness is the inability to remain awake and alert during daytime waking periods, leading to the inadvertence of drowsiness or sleep. It is estimated that ∼20% of adults experience sleepiness. Daytime sleepiness is a major public health problem because it has been linked to cognitive impairment, traffic accidents, medical negligence, and reduced productivity. In China, daytime napping is often considered a healthy lifestyle, especially for the elderly. However, studies have shown a potential relationship between daytime napping and stroke incidence (25). Daytime sleepiness, characterized by daytime naps, is considered to be an indicator of poor sleep quality or health disorders. In two studies with 9,095 participants followed up for over 5.1 years (208 stroke patients), sleepiness (ESS score ≥10) was found to be a predictor of stroke after adjusting for confounders such as age, sex, vascular risk factors, and comorbidities (25, 26). In a study of 213 stroke patients treated in a rehabilitation center, sleepiness was found to affect post-stroke rehabilitation. Patients with sleepiness had a higher rate of disability and a higher rate of transferring to a nursing home at discharge (27). The effects of sleepiness on stroke may include several aspects. First, sleepiness may be a manifestation of sleep disorders such as insufficient sleep duration or circadian rhythm disturbances, which can increase the risk of stroke. Second, sleepiness may be caused by an underlying disease that may be a risk factor for stroke. In addition, sleepiness may lead to an increase in caffeine intake, which disrupts nocturnal sleep and increases daytime sleepiness. Sports activities can improve sleep quality and reduce sleepiness, but sleepiness can lead to insufficient energy to participate in regular sports activities, which can increase the risk of stroke. However, many previous studies have shown that sleepiness is associated with poor outcomes after stroke. In our study, the effect of sleepiness assessed by the ESS scale on neurological function after stroke was not found. Further confirmation with large-scale objective measures is needed.

Studies have shown that OSA precedes stroke rather than being the consequence of stroke. A prospective study on OSA found that the incidence of OSA was consistent before and after stroke, suggesting that OSA is a common inducing factor (28). Previous studies have found no association between the prevalence or severity of OSA and stroke subtypes or stroke severity. The Wisconsin cohort study, which included 1,189 healthy participants, showed that sleep-related apnea-hypopnea index (AHI) ≥20/h was associated with an increased risk of stroke over the next 4 years (29). In a community-based study

TABLE 6 Univariate and multivariate COX analysis of the influencing factors of all-cause death (survivors were coded 0, and dead patients were coded 1).

		Univariate COX analysis		Multivariate COX analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Population information	Gender (male)	0.754 (0.541–1.052)	0.096	NA	
	Age	1.098 (1.080–1.117)	<0.001*	NA	
	low level of education	1.505 (1.084–2.089)	0.015*	NA	
Stroke type	TIA	1.180 (0.577–2.413)	0.651	NA	
	Cerebral infarction	0.825 (0.455–1.494)	0.525	NA	
Lesion characteristics	Dominant hemisphere	0.803 (0.574–1.123)	0.199	NA	
	Large lesion	1.531 (0.783–2.996)	0.213	NA	
	Brainstem lesion	1.057 (0.665–1.678)	0.815	NA	
	Critical sites lesion	0.938 (0.623–1.412)	0.758	NA	
	Multiple lesions	1.435 (1.020–2.020)	0.038*	NA	
	MTA score	2.230 (1.879–2.647)	<0.001*	NA	
	Fazekas score	1.550 (1.381–1.740)	<0.001*	NA	
	Microbleeds	2.795 (2.024–3.859)	<0.001*	NA	
Arteriostenosis	ICA	1.967 (1.407–2.750)	<0.001*	1.871 (1.192–2.937)	0.007
	MCA	1.488 (1.074–2.064)	0.017*	NA	
	ACA	1.682 (1.026–2.756)	0.039*	NA	
	VA	2.018 (1.449–2.811)	<0.001*	NA	
	BA	2.609 (1.811–3.757)	<0.001*	1.725 (1.095–2.717)	0.019
Risk factors	Hypertension	0.847 (0.595–1.205)	0.356	NA	
	Coronary heart disease	2.126 (1.521–2.971)	<0.001*	NA	
	Diabetes	1.125 (0.797–1.587)	0.503	NA	
	Drinking	0.422 (0.290–0.614)	<0.001*	NA	
Blood pressure and heart rate	Smoking	0.484 (0.343–0.684)	<0.001*	NA	
	Systolic pressure	1.007 (1.003–1.012)	0.002*	NA	
	Diastolic pressure	0.982 (0.970–0.994)	0.002*	NA	
	Heart rate	1.008 (0.995–1.022)	0.248	NA	
Laboratory examination	Hcy	0.980 (0.955–1.006)	0.125	NA	
	FBG	1.028 (0.973–1.086)	0.324	NA	
	TG	0.836 (0.691–1.012)	0.066	NA	
	TC	1.000 (0.993–1.007)	0.991	NA	
	HDL	1.146 (0.815–1.613)	0.434	NA	
	LDL	0.997 (0.982–1.013)	0.741	NA	
Patients status at admission	MoCA score	0.931 (0.911–0.951)	<0.001*	NA	
	Depression	1.462 (0.988–2.162)	0.057	NA	
	NIHSS score	1.117 (1.069–1.167)	<0.001*	NA	
	Low sleep quality	1.899 (1.313–2.746)	0.001*	NA	
	Sleepiness	1.304 (0.917–1.856)	0.139	NA	
	High risk OSA	25.185 (3.223–196.810)	0.002*	1.582 (1.244–2.012)	<0.001
	Nocturnal TST (<7 h)	3.892 (2.142–7.070)	<0.001*	NA	
	nocturnal TST (>8 h)	3.755 (1.910–7.385)	<0.001*	NA	
Characteristics of cases	Wake–up stroke	1.028 (0.986–1.072)	0.188	NA	
	END	0.916 (0.195–4.315)	0.912	NA	

*$p < 0.05$, items with statistical significance in univariate analysis were included in the multivariate logistic regression analysis.

of 5,422 healthy participants without stroke who were assessed for PSG with a mean follow-up of 8.7 years, participants with an AHI>15/h were shown to have a 30% higher risk of stroke (30). A meta-analysis of 17 population-based prospective cohort studies showed that moderate to severe OSA significantly increased the risk of stroke (RR 2.02, 95% CI 1.4–2.9) (31). OSA is not only an independent risk factor for stroke but is also associated with a poor prognosis of stroke and an increased risk of stroke recurrence and death. OSA can induce stroke recurrence, increase the risk of death, and have a negative impact on the prognosis of stroke. In a prospective cohort study of 166 patients with ischemic stroke, 96 (58%) patients with AHI ≥20/h were provided with continuous positive airway pressure (CPAP) (32). 7 years later, patients with more severe OSA who could not tolerate CPAP had a significantly increased risk of non-fatal cerebrovascular disease (CVD) and recurrent stroke compared with patients without OSA or with mild OSA supported by CPAP. OSA may be a predictor of poor neurological function after stroke. OSA increases the risk of short-term neurological decline and long-term neurological dependence. In a study of 41 patients with acute ischemic stroke, OSA severity was associated with acute stroke severity and mRS score at discharge (33). The mechanism by which OSA causes poor neurological function after stroke is unclear, but it may be related to the damage of OSA to brain tissue, including the effect of sleep fragmentation on cognitive function and the effect of intermittent hypoxemia on ischemia and neuroplasticity. There are little data on the long-term effects of OSA treatment in patients with ischemic stroke or TIA. However, some current studies have shown that early OSA treatment can improve the prognosis of stroke, including stroke severity, neurological status, and recurrence (34). OSA may affect the prognosis of stroke in several ways. The direct effects of apnea are decreased oxygen saturation, sympathetic activation, and elevated blood pressure. In addition, OSA is associated with insulin resistance, dyslipidemia, elevated systemic inflammation, hypercoagulability, and impaired endothelial function, which may influence the prognosis of stroke. A prospective 10-year follow-up study of stroke rehabilitation patients found that OSA patients had a significantly higher risk of death than controls (35). Another study found that OSA patients had a 2-fold increased risk of stroke or all-cause death over 3.4 years, independent of known vascular risk factors, and the risk of stroke or all-cause death increased with the increase of OSA severity (36). Our study did not find an association between the high risk of OSA and poor neurological function after stroke but found that the high risk of OSA was a risk factor for all-cause death after stroke.

Early neurological function is also poor when there is intracerebral hemorrhage, large lesions, or multiple lesions. These patients have more severe neurological impairment at the onset and a poor prognosis of early neurological function. Patients with high MTA scores and Fazekas scores had a poor neurological outcome due to a higher percentage of patients with high MTA scores and Fazekas scores with cognitive impairment, which is closely associated with poor neurological outcomes. Stroke patients with ICA stenosis, BA stenosis, and END have a severe illness, poor prognosis, and high mortality, so ICA stenosis, BA stenosis, and END are associated with poor neurological outcomes.

Conclusion

Low sleep quality, nocturnal TST (<7 h), and nocturnal TST (>8 h) were associated with poor neurological function after stroke. A high risk of OSA was associated with a higher risk of all-cause death after stroke.

Limitations

We did not diagnose sleep disorders through objective tests but through the PSQI questionnaire, ESS questionnaire, Berlin questionnaire, and STOPBANG questionnaire, which may have potential deviations. However, many studies have proven these scales to be reliable screening measures for sleep disorders. More importantly, our investigators are highly trained, and the study also included comprehensive information on sleep disorders and longitudinal follow-up, which may make the results more accurate.

In future research, we need to further improve the evaluation methods for sleep disorders and use objective evaluation methods when conditions permit. The relationship between sleep disturbance and cognitive changes after stroke was further investigated. The pathological significance and molecular mechanisms of non-respiratory related sleep disorders secondary to stroke are not well-understood and need further study and confirmation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

YZ: conceptualization, methodology, software, and writing—original draft preparation. XX and TZ: data curation and writing—original draft preparation. CZ: visualization and investigation. RL and SL: supervision. YY and CZ: software and validation. WY and XL: writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Identifying longitudinal patterns of CPAP treatment in OSA using growth mixture modeling: Disease characteristics and psychological determinants

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In this study, we aim to identify the distinct subtypes of continuous positive airway pressure (CPAP) user profiles based on the telemedicine management platform and to determine clinical and psychological predictors of various patterns of adherence. A total of 301 patients used auto-CPAP (Autoset 10, Resmed Inc.) during the treatment period. Four categories of potential predictors for CPAP adherence were examined: (1) demographic and clinical characteristics, (2) disease severity and comorbidities, (3) sleep-related health issues, and (4) psychological evaluation. Then, growth mixture modeling was conducted using Mplus 8.0 to identify the unique trajectories of adherence over time. Adherence data were collected from the telemedicine management platform (Airview, Resmed Inc.) during the treatment. Three novel subgroups were identified and labeled "adherers" (53.8% of samples, intercept = 385, slope = −51, high mean value, negative slope and moderate decline), "Improvers" (18.6%, intercept = 256, slope = 50, moderate mean value, positive slope and moderate growth) and "non-adherers" (27.6%, intercept = 176, slope = −31, low mean value, negative slope and slight decline). The comorbidities associated with OSA and the apnea–hypopnea index (AHI), which reflects the objective severity of the disease, did not differ significantly among the subgroups. However, "improvers" showed higher levels of daytime sleepiness (8.1 ± 6.0 vs. 12.1 ± 7.0 vs. 8.0 ± 6.1 in SWIFT, $p = 0.01$), reduced daytime function (4.6 ± 1.6 vs. 3.8 ± 1.6 vs. 4.2 ± 1.8 in QSQ daytime symptoms, $p = 0.02$), and characteristics of positive coping style (1.8 ± 0.5 vs. 1.9 ± 0.5 vs. 1.7 ± 0.5 in SCSQ positive coping index, $p = 0.02$). Negative emotion was more pronounced in patients with "non-adherers" (12.9 ± 3.8 vs. 13.7 ± 3.3 vs. 14.6 ± 3.5, $p = 0.02$ in the HADS depression dimension; 9.0 ± 6.1 vs. 9.8 ± 5.1 vs. 11.5 ± 6.3, $p = 0.01$ with Negative Affectivity in DS14, and 9.3 ± 6.1 vs. 10.3 ± 5.1 vs. 11.7 ± 6.5, $p = 0.01$ with Social Inhibition in DS14). Overall, our study demonstrated that CPAP therapy may present distinct trajectories of adherence over time in addition to the traditional binary classification. Self-reported sleep health issues (diurnal sleepiness and daytime dysfunction) as well as psychological characteristics (negative emotions and coping style) were predictors of different adherence subtypes in patients with OSA.

Understanding CPAP use profiles and their predictors enable the identification of those who may require additional intervention to improve adherence and further enhance the therapeutic effect in OSA patients.

KEYWORDS

obstructive sleep apnea, continuous positive airway pressure, adherence patterns, growth mixture modeling, psychological characteristics, daytime sleepiness, daytime dysfunction

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive collapse of the upper airway resulting in episodic oxygen desaturations, sleep arousal, and excessive daytime sleepiness (1–3). Patients with untreated OSA are at greatly increased risk for neurocognitive decline, hypertension, cardiovascular disease, and stroke (4, 5). Continuous positive airway pressure treatment (CPAP) of OSA has been shown to be effective in reducing these risks (6–8). However, adherence to CPAP therapy, which refers to the duration of mean nightly usage, is the greatest barrier to the effective treatment of OSA (9). The threshold of 4 h per night of CPAP administered during 70% of the days monitored has been widely predefined to meet minimum standards of good adherence (10). The first study described objective patterns in adherence to CPAP therapy in OSA patients by applying a CPAP machine containing a microprocessor and monitor, and only 46% of patients met this criterion for regular use (11). However, investigators have suggested that this methodological threshold of adherence fails to take into account individual differences in patterns of adherence, thus limiting the ability of researchers to understand the complex nature of adherence behavior. Weaver et al. explored the night-to-night variability and variation in the 1st week duration of CPAP treatment and defined two use patterns named consistent user and intermittent user (12). This was the first study to emphasize the trajectories of adherence over time. However, the description of adherence continues the traditional binary classifications of good or poor, and statistical techniques have never been employed to explore multiple characterizations of patterns with CPAP use.

Recently, several approaches have been used to evaluate profiles of CPAP use over time, which described a long-term time-series trend of adherence. Aloia et al. extracted the CPAP treatment data of 71 patients with OSA and identified seven different adherence trajectories using time series analysis (13). Another study involved a sample of 161 participants. Four longitudinal patterns (great users, good users, low users, and slow decliners) of treatment subgroups were identified by time series analysis combined with dynamic cluster analysis (14). However, this approach requires a sufficient amount of data, such as the daily night usage time of CPAP with OSA patients, and the sensitivity to mean changes with dynamic cluster analysis is weak, which may result in a lack of recognition among subtypes. In addition, the complicated procedure for identifying the user subtypes may reduce the practicality of this approach in clinical work. One study conducted by Sampaio et al. (15) optimized the traditional dichotomies of previous adherence patterns and created a usage gradient named "great adherent," "moderately adherent," and "poorly adherent." Some studies have obtained three similar categories using an empirically driven analysis approach (16, 17). In Wohlgemuth's study, three CPAP user profiles labeled "non-adherers," "attempters," and "adherers" were identified based on the adherence data of the cross-section of the last follow-up node using latent profile analysis (LPA). Different from LPA, growth mixture modeling (GMM) is used to examine unique longitudinal trajectories with repeated follow-up measures. With the advantages of capturing inter-and-intra-individual differences over time, GMM has been extensively used to identify patterns of medication non-adherence. However, the longitudinal changing trajectories of adherence to CPAP treatment need to be further investigated.

Refined classifications of adherence changing patterns may contribute to deeply exploring the predictive factors affecting adherence and guide clinical intervention. To date, studies targeting predictors may still focus on binary classifications of adherence (18, 19). Factors that have been identified included the following overlapping domains: disease-related characteristics (20–22), psychological or behavioral factors (23), and technical/equipment-related factors. Severe daytime sleepiness has been shown to be an independent predictor of long-term good adherence in OSA patients (24). In addition, psychological traits such as depression and anxiety emotions in OSA patients have also been increasingly noticed by researchers to be a major obstacle to CPAP use (25–27). A better understanding of CPAP usage profiles makes it possible to distinguish the predictors of adherence patterns, particularly those amenable to interventions, so as to promote the healthy behavior of regular CPAP use.

In this study, our primary aim was to provide a description of the adherence profile of CPAP users with OSA using outcome variables from the CPAP treatment telemedicine management

platform. We applied growth mixture modeling to evaluate the distinct subtypes of CPAP users. Second, we included covariates in our analysis to explore the relationship between baseline characteristics and adherence patterns of OSA patients. Thus, interventions targeting specific subtypes may be figured out to increase the possibility of transferring non-adherents to adherents and enhance the therapeutic effect of CPAP with OSA patients.

Methods

Participants

The sample consisted of 301 patients who were newly diagnosed patients with OSA and prescribed CPAP treatment aged 18 years or more at Peking University People's Hospital from March 2019 to May 2022. According to the diagnosis and treatment guidelines of OSA recommended by the American Academy of Sleep Medicine (AASM), patients with apnea hypopnea index (AHI) ≥5 times/h combined with severe symptoms (sleepiness, cognitive dysfunction), or AHI > 15 times/h were recruited and assigned to CPAP treatment. All patients underwent a standardized telemedicine diagnosis and treatment protocol that included general clinical evaluation, home sleep test, questionnaires evaluation of disease symptoms and psychological traits and CPAP treatment. During the period of CPAP treatment, sleep physicians will review the adherence data of CPAP treatment for OSA patients *via* a telemedicine management platform at 1 week, 1 month, and 3 months and follow up by telephone. Sleep specialists evaluated the response of participants to CPAP treatment, asked if there were obstacles restricting CPAP use, and provided suggestions on how to overcome these problems. In addition, participants were asked to complete questionnaires evaluating the improvements in symptoms after treatment at 1 month. This research was approved by the Medical Ethics Committee of Peking University People's Hospital (2015PHB187-01).

Procedures

Sleep test

The type 3 portable monitoring device NOXT3 (Nox Medical, Reykjavik, Iceland) was used to diagnose OSA in our study, which records nasal airflow, thorax and abdominal respiratory efforts, pulse oximetry, air pressure, and body position (28). The scoring of sleep tests was completed by sleep technologists in accordance with the American Academy of Sleep Medicine (AASM). Apnea was defined as a decrease of ≥90% in the peak value of respiratory airflow signal compared with the baseline and a decrease duration of ≥10 s. Hypopnea was defined as a decrease of ≥30% in the peak value of respiratory airflow signal compared with the baseline and a decrease of ≥3% in oxygen saturation (29). The apnea hypopnea index (AHI) is the number of respiratory events per hour in the HSAT. According to the international classification of sleep disorders, patients with AHI ≥5 events/h and OSA-related symptoms such as sleepiness, hypertension or type 2 diabetes were diagnosed with OSA (30).

CPAP treatment initiation

The participants diagnosed with OSA received CPAP (Autoset 10^{TM} Plus C, Resmed, Australia) and underwent a standardized, 30-min mask fitting and equipment educational session conducted by the CPAP technician. The sleep physician helped choose a mask (migrate FX, Resmed, Australia) and introduced the working principle of CPAP, the benefits of treatment, and how to avoid and deal with possible side effects. The CPAP pressure setting was 6–20 cm H_2O. All Resmed S10 CPAP devices have a mobile communication chip that connects to the telemedicine monitoring cloud platform, which transmits CPAP treatment data in real time automatically. Patient adherence and therapy data are uploaded to the platform daily, typically within 1 h after each therapy session. It enables healthcare professionals to quickly access patient data, share clinical insights with other health professionals, and help patients solve problems during ventilator treatment in time. Sleep physicians will help patients complete their registration on the platform. The information provided includes usage data (hours of daily use and days used per month) and therapy issues (e.g., therapeutic modalities, mask leak, residual AHI, and type of apnea). Residual AHI is defined by an apnea-hypopnea index after CPAP therapy (the normal residual AHI ≤ 5 events/h).

Outcome measures

Demographic characteristics, comorbidities, self-reported disease severity, and psychological assessment were recorded at baseline. Self-reported daytime sleepiness, fatigue, and insomnia were measured using the Epworth Sleepiness Scale (ESS), Sleepiness-Wakefulness Inability and Fatigue Test (SWIFT), and Insomnia Severity Index (ISI). The impact of daytime sleepiness on activities of daily living was measured by the Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10), Pittsburgh Sleep Quality Index (PSQI), and Quebec Sleep Questionnaire (QSQ). Psychological assessment mainly included anxiety and depression symptoms, personality, and familiar coping characteristics in OSA patients, using the Hospital Anxiety and Depression Scale (HADS), Type D Personality Scale-14 (DS-14), and Simplified Coping Style Questionnaire (SCSQ). The use of CPAP was recorded from the telemedicine monitoring cloud platform.

Questionnaires

(1) ESS: ESS was developed to assess the degree of daytime sleepiness of patients. The instrument has eight items. The probability of dozing in each question is "never," "mild," "moderate," and "severe." The scores are 0, 1, 2, and 3. The maximum total score is 24. If the total score is more than 9, the patient is considered to have daytime sleepiness and risk of OSA. The split-half reliability coefficient and Cronbach's alpha coefficients of the Chinese version of the ESS were 0.81 and 0.80, respectively (31).

(2) SWIFT: the SWIFT is 12-item questionnaire with two subscales measuring sleepiness-wakefulness inability and fatigue. Subscale A involves six questions related to difficulty staying awake/wakefulness inability in different situations that might affect performance or cause adverse consequences; Subscale B has six questions related to fatigue, tiredness, or lack of energy in different situations. All scales require a 4-level (0–3) Likert response, and higher scores indicate lower wakefulness, higher fatigue, or lack of energy (32).

(3) ISI: The ISI assesses the subjective severity of insomnia in the past 2 weeks. It consists of seven items, each of which has a score of 0–4, with higher scores indicating more severe insomnia. The Chinese version of the ISI was verified by Chung et al. (33), and Cronbach's alpha coefficients and retest reliability were 0.83 and 0.79, respectively.

(4) FOSQ-10: FOSQ-10 was adapted by Weaver in 2009 (34). By selecting the items of the original FOSQ-30, 10 items and 5 dimensions were finally determined, including general condition (two items), activity level (three items), vigilance (three items), social outcome (one item), and intimacy and sexual relations (one item). Each item is set with four options of "very difficult, moderately difficult, somewhat difficult, and no difficult," and the score is scored on a scale of 1–4. The total score is the average score of each dimension multiplied by 5, and the total score is 20. The higher the score, the better the daytime functional status of OSA patients. The Cronbach's alpha coefficient of the scale was 0.84, and the test-retest reliability was 0.73.

(5) QSQ: The QSQ is a specific quality of life scale for OSA that is designed to evaluate the effect of clinical treatment. The QSQ is a self-rating scale with 5 dimensions and 32 items, including daytime sleepiness, daytime symptoms, nighttime symptoms, mood changes, and social interaction. The item score is 1–7 using the Likert 7-point scoring method. The score of each dimension is equal to the sum of the scores of items in the dimension divided by the number of items in the dimension. The total score of QSQ is the sum of the mean scores of the five dimensions divided by 5. The higher the score, the better the quality of life (35).

(6) PSQI: The PSQI evaluates seven domains: (a) sleep quality; (b) latency; (c) duration; (d) habitual sleep efficiency; (e) use of medications; (f) disturbance; and (g) daytime dysfunction. The scores from these domains can be summed to produce a global score. The total score ranges from 0 to 2l, and higher scores indicate the worse quality of sleep. Liu et al. introduced it in China in 1996 and proposed that the PSQI was suitable for sleep quality evaluation research in China because of its simplicity, high reliability, and validity, with Cronbach's alpha coefficients of 0.84.

(7) DS14: As a standard assessment tool for distressed personality, the Type D Personality Scale is simple and easy to operate. It contains two dimensional characteristics: negative affect (NA) and Social Inhibition (SI). When the scores of NA and SI are >10, it means a higher level of negative emotions such as anxiety, irritability, and pessimism and a tendency to inhibit the expression of negative emotions in social interaction (36).

(8) HADS: The HADS is a 14-item scale with two subscales measuring anxiety and depression on a four-point (0–3) Likert scale. Scores range from 0 to 21 on both scales. A score above 11 (cut-off threshold) indicates a clinical diagnosis of anxiety and depression. The internal consistency reliability coefficient was adequate for both anxiety (Cronbach's alpha coefficient = 0.72) and depression subscales (Cronbach's alpha coefficient = 0.82), indicating good reliability (37).

(9) SCSQ: The SCSQ was compiled by Xie (38) and included 20 items divided into two dimensions: positive coping and negative coping. The positive coping dimension consists of items 1–12, and the negative coping dimension consists of items 13–20. The questionnaire was self-rated with a four-level Likert scale ranging from "do not use" to "often use," with 0–3 points each. The results were divided into positive coping scores and negative coping scores. The higher the score of positive coping, the more inclined the respondents were to adopt a positive coping style. The higher the negative response score is, the more inclined the respondents are to adopt a negative coping style (39).

CPAP adherence evaluation

In this study, we assessed data from a large cloud database (AirView^{TM}) of the continuous positive airway pressure (CPAP) management system to examine adherence to therapy from March 2019 to May 2022. Patient adherence and therapy data are uploaded daily, typically within 1 h after each therapy session. Adherence typically refers to the consistency with which a patient uses PAP therapy. Mean daily use (hours) on all days =

total hours of PAP used/total number of follow-up days. Mean daily use on days PAP used = total hours of PAP used/total days used during follow-up. The most widely recognized criterion for adherence is the usage of a PAP device for ≥4 h per night on at least 70% of nights (10). In our study, we extracted the mean daily use of CPAP in 1 week, 1 month, and 3 months, and plotted as continuous changing trajectories. Based on this, we could classify and further understand the subtypes of CPAP adherence.

Statistical analysis

Data for continuous variables as presented were compared across the three clusters using the ANOVA *F*-test or Kruskal–Wallis test, depending on the distribution of data. Proportions are presented as percentages and were compared with the χ^2-test. The relationship between putative predictive variables and subsequent adherence clusters was assessed using multinomial logistic regression. Odds ratios (OR) of subgroup membership were estimated for each predictor. Such analysis aims to predict the dependent variables of subtypes (in this case, adherent/non-adherent/improvers) on the basis of categorical or continuous independent variables. All tests were conducted using the Statistical Package for the Social Sciences (SPSS) version 24.0 (SPSS, Chicago, IL, USA). We also describe the trend curve of adherence over time. The present study employed growth mixture models (GMMs) to determine distinct, homogeneous, and longitudinal trajectories in the use of PAP over the 3 months of follow-up. The advantage of GMM is to probabilistically identify homogenous subgroups within larger heterogeneous memberships and represent unobserved heterogeneity by inferring each individual's membership to latent classes from the growth model data (40). MPlus v.8.0 (Los Angeles, CA) was used for all GMM analyses. The model fit between 1 and 4 trajectories was compared (k vs. k-1 trajectories) using the Lo-Mendell Rubin adjusted likelihood ratio test (LRT, $p<0.05$), Parametric Bootstrapped Likelihood Ratio Test (BLRT, $p < 0.05$), Bayesian Information Criteria (BIC), Akaike information criterion (AIC), and convergence (entropy closest to 1.0).

Results

Characterization of longitudinal patterns of CPAP users

A total of 301 diagnosed patients with OSA who used CPAP regularly were recruited in this study. Growth Mixture Models were evaluated with the number of possible classes ranging from one to four to identify the longitudinal trajectories over time. We used the average daily usage time as the evaluation indicator. Fit indexes for all models are presented in Table 1. Across all models, entropy values ranged from 0.76 to 0.85, indicating a good fit to the data in two to four cluster solutions. The AIC, BIC, and aBIC were observed to decrease as the number of clusters extracted increased, suggesting that a greater number of clusters fit the data progressively better. The LRT test, however, suggested that the three-cluster solution was the best-fitting model, as it was shown to perform significantly better than the four-cluster solution ($p < 0.001$ in cluster 3 and $p = 0.59$ in cluster 4). Therefore, the three-cluster solution was selected as the best representation of the data. The three subgroups identified were labeled "non-adherers," "improvers," and "adherers" based on their means of adherence indicators and variation tendency characteristics. The "non-adherers," "improvers," and "adherers" subgroups comprised 27.6% ($n = 83$), 18.6% ($n = 56$), and 53.8% ($n = 162$) of the sample, respectively. Trajectories of means on the three adherence variables were determined using minutes on the CPAP every night. Cluster 1 showed high adherence in the 1st week and decreased slightly during the follow-up period and was categorized as the high adherence group (adherers; I = 385, S = −51); cluster 2 presented lower adherence in the 1st week compared with cluster 1 but showed a gradual increase in the following time, so it was the subtypes with improved adherence (improvers; I = 256, S = 50); cluster 3 had low adherence in the 1st week and continued to decline during the follow-up period and was named the low adherence group (non-adherers; I = 176, S = −31; see Figure 1). A comparison of the usage data (nightly use in minutes, the proportion of good adherence, percentage of nights with ≥4 h usage) and therapy issues (e.g, therapeutic pressure, mask leak, residual AHI) among groups was presented in Table 2. The proportion of days compliant and usage time per night at 3 months was 68.8%, 281.4 min; 73.8%, 365.0 min, and 25.7%, 107.7 min, respectively. All groups showed significant improvements after CPAP treatment, and there was no significant difference in residual AHI (2.5 ± 1.8 vs. 2.4 ± 1.8 vs. 2.6 ± 2.0 events/h, $p = 0.92$; see Table 2).

TABLE 1 Fit indices for growth mixture modeling analysis.

						P	
Method	**Cluster**	**AIC**	**BIC**	**aBIC**	**Entropy**	**LRT**	**BLRT**
GMM	1	9,958.16	9,976.12	9,960.27	/	/	/
	2	9,825.98	9,854.71	9,829.34	0.76	0.00	0.00
	3	9,789.48	9,839.75	9,795.36	0.84	0.00	0.00
	4	9,819.14	9,858.64	9,823.76	0.85	0.59	0.59

AIC, Akaike information criterion; BIC, Bayesian information criterion; aBIC, sample-size-adjusted BIC; LRT, Lo-Mendell Rubin adjusted likelihood ratio test; BLRT, Parametric Bootstrapped likelihood ratio test ratio test.

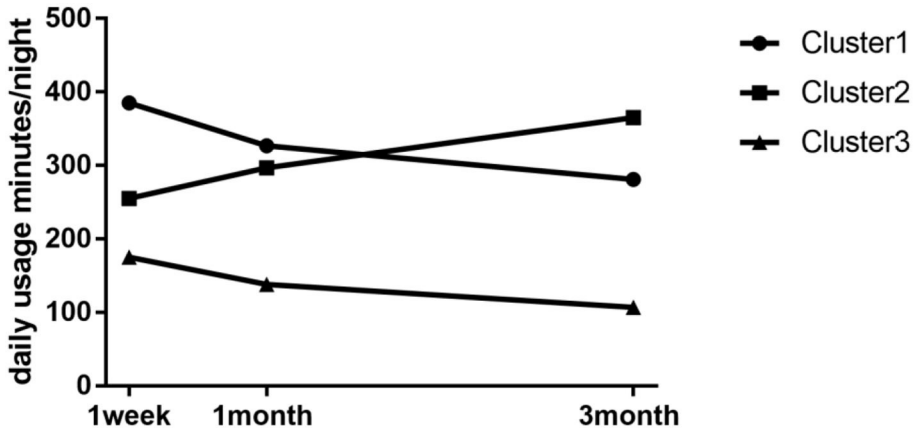

FIGURE 1
Patterns of longitudinal adherence to CPAP during 3 months treatment. Cluster 1 = adherers; Cluster 2 = improvers; Cluster 3 = non-adherers.

TABLE 2 Comparison of treatment effect and adherence of three subtypes.

	1 week					1 month					3 months				
	Cluster 1 $N = 162$	Cluster 2 $N = 56$	Cluster 3 $N = 83$	F/X^2	p	Cluster 1 $N = 162$	Cluster 2 $N = 56$	Cluster 3 $N = 83$	F/X^2	p	Cluster 1 $N = 162$	Cluster 2 $N = 56$	Cluster 3 $N = 83$	F/X^2	p
Proportion of good compliance, %	149 (92.0)	22 (39.3)	14 (16.9)	144.9	0.00	111 (68.5)	20 (35.7)	2 (2.4)	99.0	0.00	88 (54.7)	40 (71.4)	0 (0.00)	91.7	0.00
Proportion of days compliant (usage ≥4 h/night), %	87.1 ± 15.2	59.4 ± 19.2	40.5 ± 20.5	203.0	0.00	75.9 ± 18.4	64.9 ± 16.9	30.9 ± 16.2	179.0	0.00	68.8 ± 19.2	73.8 ± 12.3	25.7 ± 15.6	201.0	0.00
Device usage (used days), mins/night	391.7 ± 74.6	317.5 ± 73.9	241.0 ± 76.9	111.0	0.00	362.7 ± 68.0	323.7.2 ± 76.3	217.2 ± 79.5	109.0	0.00	332.4 ± 72.7	388.4 ± 57.6	185.2 ± 88.6	150.0	0.00
Daily usage (all days), mins/night	385.1 ± 62.7	255.8 ± 68.9	175.5 ± 53.7	337.6	0.00	327.9 ± 78.6	293.2 ± 72.7	138.4 ± 55.4	202.0	0.00	281.4 ± 76.7	365.0 ± 71.4	107.7 ± 54.4	266.0	0.00
95% pressure, cm H_2O	10.9 ± 1.8	11.2 ± 1.9	10.6 ± 2.2	1.4	0.20	10.9 ± 1.9	10.9 ± 1.8	10.6 ± 1.9	0.5	0.50	10.9 ± 1.9	10.7 ± 1.4	10.9 ± 1.9	0.3	0.70
95% mask leak, L/min	17.5 ± 11.4	18.5 ± 10.4	15.4 ± 11.0	0.1	0.90	18.4 ± 11.0	18.7 ± 9.7	16.1 ± 10.6	0.1	0.80	19.1 ± 11.9	20.2 ± 9.7	19.2 ± 10.8	0.4	0.60
Residual AHI, events/hour	3.2 ± 2.7	3.0 ± 2.2	3.2 ± 3.0	0.1	0.95	2.6 ± 2.0	2.6 ± 1.8	2.8 ± 2.2	0.2	0.80	2.5 ± 1.8	2.4 ± 1.8	2.6 ± 2.0	0.1	0.92

Characteristics of demographics, comorbidities, disease severity, and associations with adherence subtypes

The study sample consisted of 301 individuals. The participants were predominantly male (91.3%) and had a mean age of 44.3 years and a mean BMI of 28.4 kg/m^2. Descriptive characteristics of the study sample are presented in Table 3. Participants in all CPAP user subgroups were similar in terms of age, sex, BMI, educational background, marital status, smoking, and drinking status. However, economic status ($\chi^2 = 25.2$, $p < 0.01$) and physical exercise ($\chi^2 = 45.7$, $p < 0.01$) differed significantly among the subtypes. Participants in cluster 1 and cluster 2 had healthier lifestyles and were significantly more

TABLE 3 Demographic characteristics of three patterns of adherence.

	Cluster 1 $N = 162$	Cluster 2 $N = 56$	Cluster 3 $N = 83$	F/X^2	p
Age	45.3 ± 11.2	43.5 ± 10.6	44.1 ± 12.0	0.65	0.50
Sex				2.15	0.35
Male	146 (90.1)	50 (89.3)	79 (95.2)		
Female	16 (9.9)	6 (10.7)	4 (4.8)		
BMI kg/m^2	28.5 ± 3.7	28.7 ± 3.1	28.0 ± 3.6	0.72	0.48
Education				4.80	0.27
High school or lower	26 (16)	10 (17.9)	17 (20.5)		
Some college	9 (5.6)	6 (10.7)	10 (12)		
College grad or higher	127 (78.4)	40 (71.4)	56 (67.5)		
Economic				25.20	0.00
Lower	31 (19.1)	5 (8.9)	26 (31.3)		
Middle	107 (66)	33 (58.9)	53 (63.9)		
High	24 (14.8)	18 (32.1)	4 (4.8)		
Medical insurance				7.60	0.42
Medical insurance for urban employees	116 (71.6)	41 (73.2)	61 (73.4)		
Socialized medicine	36 (22.2)	9 (16.1)	12 (14.4)		
Commercial insurance	10 (6.2)	6 (10.7)	10 (12.2)		
Marital status				3.50	0.75
Spinsterhood	23 (14.2)	6 (10.7)	15 (18.1)		
Married	130 (80.2)	48 (85.7)	66 (79.5)		
Divorced	9 (5.6)	2 (3.6)	2 (2.4)		
Physical exercise				46.7	0.00
Hardly ever	19 (11.7)	12 (21.4)	33 (39.8)		
Occasionally	101 (62.4)	31 (55.3)	45 (54.2)		
Frequently	42 (25.9)	13 (23.3)	5 (6.0)		
Smoking				0.80	0.93
No	97 (59.9)	31 (55.4)	45 (54.2)		
Yes	50 (30.9)	19 (33.9)	29 (34.9)		
Quit smoking	15 (9.3)	6 (10.7)	9 (10.8)		
Drinking				1.30	0.85
No	76 (46.9)	24 (42.9)	40 (48.2)		
Yes	83 (51.2)	31 (55.4)	40 (48.2)		
Quit drinking	3 (1.9)	1 (1.7)	3 (3.6)		

BMI, Body Mass Index.

likely to engage in prolonged physical activity than participants in cluster 3 (the percentage of participants who exercised frequently was 25.9% in cluster 1, 23.3% in cluster 2, and 6.0% in cluster 3). In addition, participants who reported better economic conditions were significantly more likely to belong to the "adherers" and the "improvers" (see Table 3).

TABLE 4 Characteristics of comorbidities and disease severity among three clusters.

	Cluster 1 $N = 162$	Cluster 2 $N = 56$	Cluster 3 $N = 83$	F/X^2	p
Mallampati score				6.31	0.39
I	21 (13)	9 (16.1)	10 (12.0)		
II	58 (35.8)	25 (44.6)	29 (34.9)		
III	41 (25.3)	13 (23.2)	16 (19.3)		
IV	42 (25.9)	9 (16.1)	28 (33.8)		
AHI	42.8 ± 34.1	40.0 ± 22.7	37.4 ± 20.5	0.92	0.38
ODI3	37.7 ± 21.9	37.1 ± 21.0	33.7 ± 18.6	1.00	0.35
Mean SpO_2	92.2 ± 2.7	92.1 ± 2.5	92.5 ± 2.7	0.41	0.61
Lowest SpO_2	74.8 ± 9.5	73.8 ± 9.7	75.1 ± 8.5	0.32	0.68
Hypertension	78 (48.1)	22 (39.3)	41 (46.8)	1.61	0.45
Hyperlipidemia	48 (29.6)	12 (21.4)	20 (24.1)	1.72	0.41
Heart disease	7 (4.3)	1 (1.8)	2 (2.4)	1.13	0.52
Stroke	2 (1.2)	0 (0)	3 (3.6)	3.01	0.17
COPD	2 (1.2)	2 (3.6)	2 (2.4)	1.20	0.62
Diabetes	16 (9.9)	4 (7.1)	5 (6.0)	1.10	0.56
Thyroid disease	12 (7.4)	2 (3.6)	6 (7.2)	4.11	0.38
Hypertension medication	45 (27.8)	14 (25)	29 (34.9)	4.91	0.28
Rhinitis	16 (9.9)	6 (10.7)	9 (10.8)	0.17	0.90
Hyperuricemia	29 (17.9)	14 (25.0)	26 (31.3)	5.70	0.06
High frequency of snoring	119 (73.5)	45 (80.4)	55 (66.3)	4.40	0.62
Loud snoring	119 (73.5)	44 (78.6)	58 (69.9)	3.80	0.70

AHI, Apnea–hypopnea index; ODI3, 3% Oxygen desaturation index; SpO_2, Oxygen saturation; COPD, Chronic obstructive pulmonary disease.

Characteristics of comorbidities and disease severity were also assessed to investigate the potential predictors of trajectories. With reference to disease severity, the groups did not differ significantly on any of the apnea hypopnea index (AHI) or 3% oxygen desaturation index (3% ODI). The mean AHI and 3% ODI in the three clusters were 42.8 ± 34.1 events/h, 40.0 ± 22.7 events/h, 37.4 ± 21.9 events/h with AHI; and 37.7 ± 21.9 events/h, 37.1 ± 21.0 events/h, 33.7 ± 18.6 events/h with 3% ODI. The proportion of comorbidities with OSA in our sample was high with hypertension, hyperlipidemia, and hyperuricemia. The average rate of self-reported hypertension

TABLE 5 Sleep-related health issues at baseline and 1 month among three clusters.

	Cluster 1 ($N = 162$)	Cluster 2 ($N = 56$)	Cluster 3 ($N = 83$)	F/X^2	p
ESS					
Baseline	11.5 ± 5.2	12.5 ± 5.5	10.3 ± 4.8	2.62	0.07
1 month	8.1 ± 4.6	10.2 ± 4.7	9.7 ± 4.5	4.85	0.00
Change	3.3 ± 4.9	2.2 ± 4.0	0.5 ± 2.5	1.26	0.28
FOSQ-10					
Baseline	15.6 ± 3.0	15.1 ± 4.2	15.2 ± 3.7	3.20	0.76
1 month	17.0 ± 3.4	16.7 ± 2.1	16.1 ± 5.4	8.20	0.09
Change	−1.4 ± 2.2	−1.6 ± 2.4	−0.8 ± 2.5	1.44	0.23
PSQI					
Baseline	6.5 ± 2.8	7.5 ± 2.8	6.2 ± 2.5	1.45	0.07
1 month	4.9 ± 2.5	6.1 ± 2.6	5.7 ± 2.9	1.76	0.55
Change	1.5 ± 2.5	1.3 ± 2.1	0.5 ± 1.7	3.48	0.03
ISI					
Baseline	10.1 ± 5.4	10.8 ± 5.0	10.5 ± 6.1	0.14	0.78
1 month	6.7 ± 4.6	7.5 ± 4.9	8.4 ± 5.3	2.58	0.07
Change	3.4 ± 4.7	3.2 ± 4.3	2.1 ± 4.4	1.4	0.24
SWIFT_Total					
Baseline	8.1 ± 6.0	12.1 ± 7.0	8.0 ± 6.1	9.13	0.01
1 month	4.8 ± 4.7	6.5 ± 5.1	7.2 ± 5.2	6.10	0.03
Change	3.3 ± 6.9	5.6 ± 6.6	0.7 ± 5.8	7.80	0.01
SWIFT_A					
Baseline	3.1 ± 3.0	5.2 ± 3.7	3.2 ± 2.7	9.10	0.01
1 month	1.6 ± 2.4	3.4 ± 3.3	3.6 ± 3.1	14.7	0.01
Change	1.5 ± 3.4	1.8 ± 3.9	−0.42 ± 2.4	9.22	0.00
SWIFT_B					
Baseline	4.9 ± 3.2	6.7 ± 3.6	4.7 ± 3.3	9.10	0.01
1 month	3.1 ± 3.1	3.0 ± 2.9	3.6 ± 3.5	14.7	0.01
Change	1.7 ± 4.3	3.7 ± 3.7	1.1 ± 4.7	9.22	0.00
QSQ_Total					
Baseline	4.6 ± 1.2	4.1 ± 1.0	4.4 ± 1.2	3.03	0.05
1 month	5.1 ± 1.0	4.3 ± 0.9	4.4 ± 0.9	17.2	0.00
Change	−0.5 ± 1.3	−0.2 ± 1.2	0.0 ± 1.2	3.80	0.02
QSQ_EDS					
Baseline	4.6 ± 1.2	4.1 ± 1.1	4.4 ± 1.2	3.87	0.05
1 month	5.0 ± 1.5	5.0 ± 1.4	4.8 ± 1.4	0.52	0.59
Change	−0.6 ± 1.9	−0.8 ± 1.9	−0.4 ± 1.8	1.22	0.29
QSQ_DaySym					
Baseline	4.6 ± 1.6	3.8 ± 1.6	4.2 ± 1.8	3.9	0.02
1 month	5.2 ± 1.9	3.9 ± 2.1	4.1 ± 1.9	9.96	0.00
Change	−0.6 ± 2.3	−0.1 ± 2.4	0.1 ± 1.9	1.852	0.15
QSQ_NightSym					
Baseline	4.2 ± 1.1	3.7 ± 1.2	4.0 ± 1.2	1.80	0.15
1 month	5.0 ± 1.2	3.9 ± 1.4	4.1 ± 1.4	17.10	0.00
Change	−0.8 ± 1.5	−0.2 ± 1.6	−0.1 ± 1.5	5.82	0.03
QSQ_Emotion					
Baseline	5.2 ± 1.3	4.6 ± 1.1	5.1 ± 1.4	2.93	0.05
1 month	5.6 ± 1.6	3.9 ± 2.0	4.9 ± 1.8	17.50	0.00
Change	−0.4 ± 1.8	0.7 ± 2.2	0.2 ± 1.8	6.336	0.02
QSQ_Social					
Baseline	4.6 ± 1.4	4.4 ± 1.2	4.6 ± 1.6	0.39	0.67
1 month	5.3 ± 1.5	4.9 ± 1.4	4.8 ± 1.7	3.10	0.04
Change	−0.7 ± 1.9	−0.5 ± 1.7	−0.1 ± 2.1	1.66	0.19

ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire-10; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; SWIFT, Sleepiness-Wakefulness Inability and Fatigue Test; SWIFT_A, Sleepiness dimension of SWIFT; SWIFT_B, Fatigue dimension of SWIFT; QSQ, Quebec Sleep Questionnaire; QSQ_EDS, Excessive daytime sleepiness dimension of QSQ; QSQ_DaySym, Daytime symptoms dimension of QSQ; QSQ_NightSym, Nocturnal symptoms dimension of QSQ; QSQ_Emotion, Emotion dimension of QSQ; QSQ_Social, Sociability dimension of QSQ.

TABLE 6 Psychological, personality, and familiar coping characteristics at baseline among three clusters.

	Cluster 1 $N = 162$	Cluster 2 $N = 56$	Cluster 3 $N = 83$	F/X^2	p
HADS-Depression	12.9 ± 3.8	13.7 ± 3.3	14.6 ± 3.5	6.37	0.02
HADS-Anxiety	10.8 ± 2.9	12.3 ± 3.1	11.7 ± 3.2	5.76	0.04
HADS-Depression	110 (67.9)	44 (78.6)	71 (85.5)	9.50	0.08
HADS-Anxiety	79 (48.8)	38 (67.9)	49 (59.0)	6.80	0.03
Type D personality	47 (29.0)	23 (41.1)	44 (53.0)	13.70	0.01
Negative Affectivity	9.0 ± 6.1	9.8 ± 5.1	11.5 ± 6.3	4.55	0.01
Social Inhibition	9.3 ± 6.1	10.3 ± 5.1	11.7 ± 6.5	4.44	0.01
Positive coping index	1.8 ± 0.5	1.9 ± 0.5	1.7 ± 0.5	3.98	0.02
Negative coping index	1.2 ± 0.4	1.1 ± 0.5	1.2 ± 0.4	0.66	0.51
Positive coping tendency	88 (54.3)	33 (58.9)	36 (43.3)	3.80	0.14

in OSA was 46.8% and 29.2% of those taking medication (see Table 4).

Sleep-related health issues, psychological evaluation, and associations with adherence subtypes

Subjective severity of OSA measured by self-reported ESS, ISI, SWIFT, and PSQI as well as OSA-related quality of life measured by FOSQ-10 and QSQ were assessed to explore sleep-related health issues across multiple groups. The longitudinal patterns of adherence were closely related to the degree of daytime sleepiness and daytime function in patients with OSA. The SWIFT scores were significantly increased in cluster 2, and the sleepiness dimensions of the QSQ were decreased in cluster 2, indicating that patients in cluster 2 had a higher level of sleepiness. For the SWIFT, the self-reported scores of "improvers" were significantly higher (12.1 ± 7.0) than "adherers" (8.1 ± 6.0) and "non-adherers" (8.0 ± 6.1; $\chi^2 = 9.13$,

TABLE 7 Multinominal logistic regression for predictors with three patterns.

	Cluster 1 vs. cluster 2		Cluster 1 vs. cluster 3		Cluster 2 vs. cluster 3	
	OR	*P*	OR	*p*	OR	*p*
ESS	**1.01**	**0.04**	0.99	0.07	1.02	0.26
PSQI	1.10	0.10	0.93	0.29	**1.10**	**0.02**
SWIFT_Total	**1.01**	**0.00**	1.00	0.90	**1.10**	**0.00**
SWIFT_A	**1.22**	**0.02**	1.06	0.50	1.15	0.16
SWIFT_B	0.97	0.96	0.94	0.47	1.05	0.57
QSQ_Total	**0.72**	**0.01**	1.14	0.31	0.83	0.23
QSQ_Emotion	**0.76**	**0.02**	0.92	0.49	0.82	0.15
QSQ_EDS	**0.74**	**0.02**	1.13	0.29	0.84	0.23
QSQ_DaySym	0.77	0.06	0.891	0.216	0.864	0.18
SWIFT_Total Change	**1.05**	**0.03**	**1.06**	**0.01**	**1.11**	**0.00**
SWIFT_A Change	1.02	0.63	**1.21**	**0.00**	**1.24**	**0.00**
SWIFT_B Change	1.11	0.06	1.03	0.37	**1.15**	**0.02**
QSQ_Total Change	1.24	0.10	**1.42**	**0.01**	0.87	0.41
QSQ_Emotion Change	**1.35**	**0.01**	0.85	0.05	1.14	0.17
QSQ_NightSym change	**1.30**	**0.01**	1.35	0.05	0.96	0.76
PSQI change	0.95	0.51	**1.23**	**0.01**	1.17	0.09
HADS-Depression	1.06	0.14	**1.14**	**0.01**	0.93	0.14
HADS-Anxiety	**1.16**	**0.02**	**1.10**	**0.02**	1.05	0.29
Negative-Affectivity	1.02	0.37	**1.07**	**0.03**	0.95	0.12
Social-Inhibition	1.03	0.25	**1.03**	**0.04**	0.96	0.20
Positive coping index	1.50	0.16	1.62	0.06	2.43	0.07

Bold indicates the dependent predict variables of subtypes.

$p = 0.01$), and sleepiness improved the most after 1 month of treatment in "improvers" (with a total change of 3.3 in clusters 1 and 5.6 in cluster 2 and 0.7 in cluster 3, $\chi^2 = 7.80$, $p = 0.01$). A similar trend was observed for sleepiness dimensions of the QSQ, with "improvers" presenting lower scores on the excessive daytime sleepiness (EDS) dimension in QSQ (4.1 ± 1.1) than "adherers" (4.6 ± 1.2) and "non-adherers" (4.4 ± 1.2) patients ($\chi^2 = 3.87$, $p = 0.05$). Except for daytime sleepiness, diurnal function also differed on any scores of FOSQ-10 or QSQ total. In the "improvers" group, the participants tended to have more complaints of poor daytime functioning, such as lacking concentration during work or taking more effort to carry out the daily tasks. The FOSQ-10 and QSQ scores were 15.1 ± 4.2 and 4.1 ± 1.0, respectively, in the "improvers" group, which were lower than those in the other two groups. In particular, scores on the diurnal symptom dimension of the QSQ were significantly lower in cluster 2 (4.6 ± 1.6 in cluster 1 vs. 3.8 ± 1.6 in cluster 2 vs. 4.2 ± 1.8 in cluster, $\chi^2 = 3.9$, $p = 0.02$), showing significant diurnal functional impairment in "improvers." In addition, "improvers" had poor sleep quality as measured by the PSQI, while insomnia symptoms did not show any difference (see Table 5).

Of the total psychological variables pooled in the analysis, those who suffered from depression or anxiety were more likely to be present in the poor adherence group. In the "non-adherers" group, scores on the depression dimension of HADS, as well as the negative emotion and Social Inhibition dimensions of type D personality, were significantly higher than those of the other two groups (HADS_depression: 12.9 ± 3.8 in cluster 1 vs. 13.7 ± 3.3 in cluster 2 and 14.6 ± 3.5 in cluster 3, $\chi^2 = 6.37$, $p = 0.02$; Negative Affectivity: 9.0 ± 6.1 in cluster 1 vs. 9.8 ± 5.1 in cluster 2 vs. 11.5 ± 6.3 in cluster 3, $\chi^2 = 4.55$, $p = 0.01$; Social Inhibition: 9.3 ± 6.1 in cluster 1 vs. 10.3 ± 5.1 in cluster 2 vs. 11.7 ± 6.5 in cluster 3, $\chi^2 = 4.44$, $p = 0.01$). In addition, there was an interesting finding about the relationship between coping styles and adherence. Regarding coping styles, participants in "improvers" had high scores of positive coping styles, revealing that they tend to take a positive attitude to solving and deal with problems in their daily life (Table 6).

Regression analysis to identify risk factors for adherence patterns

To determine if the sleep-related health issues and psychological covariates significant in univariate analysis were predictors of longitudinal CPAP adherence profiles at the 3-month follow-up, multinomial logistic regression models were created and analyzed. From our univariate analyses (Tables 5, 6). Covariates with $p < 0.1$ were retained for the multivariate analysis. Variables thought to exert influence on adherence, such as age, sex and AHI were forced as covariates into the multivariate analysis. The participants who reported excessive daytime sleepiness were more likely to belong to the "improvers" than the "non-adherers" subgroup (OR = 1.1, $p = 0.00$) and "adherers" subgroup (OR = 1.0, $p = 0.00$). This suggests that for each one point increase on the SWIFT, participants were 15% more likely to belong to the "improvers" subgroup when compared to the "non-adherers." Similarly, participants who reported greater improvement in sleepiness symptoms at 1 month were more likely to comply with good adherence (cluster 1 vs. cluster 3: OR = 1.21, $p = 0.00$; cluster 2 vs. cluster 3: OR =

1.24, $p = 0.00$). In addition, daytime dysfunction (lower score) favored an increasing adherence pattern compared to "adherers" (cluster 1 vs. cluster 2: OR = 0.72, $p = 0.01$ with QSQ total, OR = 0.76, $p = 0.02$ with QSQ depressed emotion, OR = 0.74, $p = 0.02$ with QSQ excessive daytime sleepiness). As for psychological covariates, our study found that negative emotions may be predictors of poor adherence. Compared with the "adherers" subgroup, the non-adherence group showed higher levels of depression and anxiety emotions and higher scores of Social Inhibition (cluster 1 vs. cluster 3 in HADS-Depression: OR = 1.14, $p = 0.01$; HADS-Anxiety: OR = 1.10, $p = 0.02$; Negative Affectivity: OR = 1.07, $p = 0.03$; Social-Inhibition: OR = 1.03, $p = 0.04$; see Table 7).

Discussion

CPAP adherence has been studied for decades, with studies typically focusing on average nightly adherence over the whole study period, which would lose meaningful information with averaging. Growth mixture models (GMMs) are an excellent tool to identify homogeneous subgroups of larger heterogeneous members of longitudinal data. In our study, three distinct patterns of adherence to CPAP use among adult Chinese patients with OSA in the first 3 months of therapy were identified. In addition, we considered that the feedback interaction based on the CPAP therapy remote management platform may influence the adherence of OSA patients over time, and in our analysis, a unique pattern with increasing adherence was found. We also combined demographic, clinical, self-reported sleep issues and psychological risk factors with the distinct patterns of adherence during the first 3 months of CPAP treatment. Excessive daytime sleepiness and daytime functional impairment may be typical characteristics of the "improvers." Similar to previous studies, negative emotion is a predictor of poor adherence.

Technological progress in the CPAP industry enables more accurate measurement of adherence, rather than early subjective self-reporting. The traditional interpretation of adherence is only divided into good adherence and poor adherence based on the use duration per night and the proportion of used days (the threshold is 4 h per night and 70% of usage days) (41, 42). As indicated in the introduction, simple classification conceals the individual characteristics of patients with OSA treated with CPAP (13, 15). Adherence is not immutable over time; it is too absolute to judge adherence only by a single node. In the whole treatment cycle, the use of CPAP may change due to changes in the surrounding environment. Several analytic methods have been employed to evaluate the intricacies of adherence behavior. Aloia et al. (13) used a separate time series analysis to make a qualitative judgment to categorize CPAP use patterns. Each individual's time series was graphed, and the authors used these graphs to classify the similar profile into seven groups based on a visual inspection of 1 year of use in 71 participants. Babbin et al. (14) replicated the adherence patterns from this previous study using a time series methodology. On this basis, a nomothetic technique named typology of temporal patterns (TTP) was employed to summarize the original clusters and obtained four distinct subtypes named great users, good users, low users, and slow decliners. Those analyses require repeated measurements at fixed intervals over the first 365 days of PAP treatment. Our approach differed from previous analyses in two ways. First, we incorporated growth mixture modeling to examine patterns in longitudinal data with three repeated measures to identify classes or subgroups within a population, which were empirically derived, not rationally or qualitatively derived; that is, we allowed the GMM statistical algorithm to produce the latent profiles (43). Second, we associated the trajectories with multidimensional disease manifestations of OSA patients, which helped to further understand the potential characteristics behind the complex adherence behavior.

Our GMM model showed varying patterns of CPAP use. Consistent with previous studies that considered CPAP use to be binary, we found typically "adherers" and "non-adherers" (44). First, the adherers showed excellent adherence at the beginning of the treatment; although compliance gradually declined with time, it was still considered fully treated at 3 months. The "non-adherers" only used machines for ∼176 min at 1 week, and the treatment time showed a slow downwards trend over time, with only 108 min of usage time at 3 months. In addition, our research also discovered a new cluster with increasing adherence over time. One study clustered CPAP data with the Ward linkage, the DTW dissimilarity and the Dunn index and identified six clusters; one of the clusters was similar to "improvers" in our study. The treatment adherence remained at a moderate level at the initial stage, but it showed a gradual upwards trend at the next time (45). A real-world study described the trajectories of ventilator treatment without external human intervention and divided the trajectories into good, medium, and poor adherence groups, and the overall adherence showed a downwards trend (46). Our research was based on the CPAP treatment remote management platform (47). Physicians regularly assessed the treatment reports on the platform and provided targeted solutions to the problems found. Some patients would take longer usage of CPAP after the problems are solved, thus showing a trend of improving adherence. Therefore, previous studies have declared that adherence could be established at an early stage (48–50). Timely discovery and targeted solutions to problems are crucial for establishing better CPAP treatment behavior at later stages. On the one hand, our research supported the standpoint that early adherence can be adjusted and improved. On the other hand, it would be helpful to identify early adherence change patterns by linking multidimensional characteristics (such as patient demography, disease severity, subjective feelings, emotional state, etc.) with the adherence trajectories. For

patients with adherence improvement characteristics, special attention should be given, and active intervention will have ideal effects.

In our study, we systematically evaluated the demographic and clinical covariates to further extend our understanding of the clusters and may assist in identifying sources of difficulty with adherence. Of all the covariates that we included, we did not find that the clusters were varied in age, BMI, medical comorbidities, AHI, oxygen desaturation index and other indicators objectively reflecting the severity of the disease. However, daytime sleepiness, reduced daytime function, depressed mood, and positive coping style could distinguish the clusters. We found that those with daytime sleepiness as well as those with daytime functional impairment were more likely to be improvers than either adherers or non-adherers. In the improvers group, excessive daytime sleepiness and impaired daytime function may affect their normal life, and this group has a strong desire for treatment. In addition, the impaired function of "improvers" enhanced significantly at 1 month. Daytime sleepiness was most significantly improved in cluster 2 in our study, which further promoted their willingness to use the CPAP machine regularly. The overall adherence of the patients in this group was good, although the initial use time was less than that in the adherers group. There may be a problem with the CPAP initiation. Telemedicine platform help physicians solve problems as soon as possible, and adherence showed an upwards trend later. Our results are consistent with previous studies. Daytime sleepiness symptoms are predictors of good adherence (23, 51). In this study, whether in the improvers or adherers group, daytime sleepiness was higher than that in the group with poor adherence. Additionally, in the subsequent emotional and personality analysis, we discovered that the participants in this group had positive response. One study also identified that adherent patients tended to have a more positive attitude and adaptive beliefs in CPAP treatment (44, 52). Improvers who have had CPAP treatment may accommodate the device positively and, as time passes, transition to the adherer clusters. This means that this group has a high subjective treatment intention, thus promoting the formation of their good health behavior.

In the symptom assessment of OSA, daytime function is one of the important indicators to evaluate the therapeutic effect of CPAP in patients with OSA, but studies that include daytime function as a predictor of CPAP adherence are limited (22, 53). In our analysis, daytime functional impairment does not distinguish adherers from non-adherers but does distinguish improvers from other clusters. OSA patients with better daytime function are more likely to become adherers or non-adherers. On the one hand, the group with good daytime function has more energy for regular treatment; on the other hand, the better daytime function may also give patients with poor adherence the illusion of no need for treatment.

It is essential to be aware of the psychological assessments of CPAP patients. The final covariates distinguishing the clusters are psychological factors. The literature regarding depressed mood and CPAP adherence is inconclusive. Some studies conducted in small to moderate samples have found no relationships (52, 54, 55). The significant heterogeneity of the literature limits the interpretation and comparison of results. In particular, inconsistencies in different instruments could also be misleading. Mandy et al. recommended the Hospital Anxiety and Depression Scale (HADS) as a tool for screening anxiety and depression symptoms of OSA patients, as it avoids confounders with other emotions. Similar to Mandy's study, depression was independently associated with adherence (26). Anxiety or depression emotion may be a potential target for clinicians to accurately distinguish people with good or poor adherence to CPAP therapy. Finally, personality and coping style, as two predictors of non-intervention, play an important role in the early identification of the pattern of adherence (56). Type D (distressed) personality is defined as a combination of Negative Affectivity and Social Inhibition. In Anders's study, Type D personality occurred in 30% of the patients with OSA and significantly increased the perceived frequency and severity of side effects, which significantly reduced self-reported adherence to CPAP treatment (57). Our study used objective data from the telemedicine management platform of CPAP treatment to prove the above conclusion. Previous studies have found that different family coping constructs provide important information about a family's ability to accept an OSAS diagnosis and adapt to CPAP treatment (15, 24). To our knowledge, this is the first study to examine the importance of personal coping constructs in OSA and their impact on CPAP adherence. Positive coping styles may play an important role in improving adherence to CPAP treatment.

Conclusion

In conclusion, we have identified, using growth mixture modeling, three latent clusters of CPAP users. We named the clusters adherers, improvers, and non-adherers. Improver is a new pattern of CPAP treatment adherence with the help of physicians' intervention based on telemedicine management platforms. Additionally, we evaluated the relationship between multidimensional characteristics and CPAP adherence, including socio-demography, disease severity, subjectively reported sleep-related problems, and emotional and psychological characteristics, which are important for identifying different subtypes at the initial stage of treatment. In a practical sense, the source of adherence difficulties can be identified and solved by understanding the meticulous identification of CPAP adherence patterns, which is conducive to further optimizing the adherence management system and

improving the effectiveness of CPAP treatment for patients with OSA.

Limitations

Our study has several limitations. We used a convenient sample of participants who participated in CPAP follow-up clinics within 3 months. Although early adherence to CPAP treatment is crucial, a prospective, longitudinal observation can better extend the generalizability of these findings. Additionally, our sample is representative of patients in China, the conclusions may not be directly applicable to patients with OSA in different countries.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Medical Ethics Committee of Peking University People's Hospital (2015PHB187-01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HY collected CPAP data and wrote and reviewed the manuscript. XD and SS designed research plan and analysis strategy. CZ and LX analyzed the data. FH revised the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Clinical and functional characteristics of OSA in children with comorbid asthma treated by leukotriene receptor antagonist: A descriptive study

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Background: Obstructive sleep apnea (OSA) is the most common form of respiratory disorders during sleep in children, especially those with severe asthma. However, optimal treatment of asthma might significantly improve OSA severity.

Methods: It was a cohort study including children aged >5 years old and diagnosed with asthma according to GINA (Global Initiative for Asthma). The data related to age, gender, height, weight, body mass index (BMI), clinical symptoms and medical history of asthma, spirometry (FEV_1: forced expiratory in 1 s), and exhaled nitric oxide (F_ENO) were recorded for analysis. Respiratory polygraphy (RPG) was done for each study subject to diagnose OSA and its severity.

Results: Among 139 asthmatic children, 99 patients with OSA (71.2%) were included in the present study (9.3 ± 0.2 years): 58.6% with uncontrolled asthma and 32.3% with partial controlled asthma. The mean ACT (asthma control testing) score was 19.0 ± 3.4. The most frequent night-time symptoms were restless sleep (76.8%), snoring (61.6%), sweating (52.5%), and trouble breathing during sleep (48.5%). The common daytime symptoms were irritable status (46.5%) and abnormal behavior (30.3%). The mean AHI (apnea-hypopnea index) was 3.5 ± 4.0 events/h. There was a significant correlation between BMI and snoring index ($R = 0.189$ and $P = 0.027$), bronchial and nasal F_ENO with AHI ($R = 0.046$ and $P < 0.001$; $R = 0.037$ and $P < 0.001$; respectively). There was no significant correlation between asthma level, FEV_1 and AHI. The severity of asthma and respiratory function were improved significantly after 3 months and 6 months of asthma treatment in combination with leukotriene receptor antagonist (LRA) treatment. The symptoms related to OSA were

significantly improved after treatment with LRA. The severity of OSA was decreased significantly after 3 months and 6 months of treatment.

Conclusion: The treatment of asthmatic children with comorbid OSA by LRA in combination with standard therapy for asthma could improve the control of asthma and the symptoms and severity of OSA.

KEYWORDS

asthmatic children, OSA, apnea-hypopnea index, snoring, leukotriene receptor antagonists

Introduction

Obstructive sleep apnea (OSA) is a continuous repetition of partial or complete obstruction of the upper airway during sleep resulting in hypopnea or total apnea despiting respiratory efforts (1). The incidence of OSA in children has been estimated about 2% (1–5%) (2). OSA has been found at any age with the highest age of 2–8 years and higher in male than female, and in Asians children (2, 3).

OSA and asthma are two co-diseases, both of which share the same symptoms because they are associated with airflow limits and increased respiratory exertion, as a result of narrowing the airways during sleeping (4). In patients with asthma, OSA plays a role as a harmful contributing factor for worsening asthma due to sleep disturbance, decreased sleep quality, destabilized bronchial tonus during sleep, increased microarousal and wake-up, and daytime sleepiness (5). Increased abdominal pressure during OSA period also contributes to gastroesophageal reflux, increased reactivity of the bronchi inducing bronchial hyperreactivity (6). Patients with hard-to-control asthma may have an increase in the number of stages with OSA and a decrease in blood oxygen saturation, especially during sleep phases with rapid eye movement (7). In children, OSA causes nocturnal intermittent hypoxia due to apnea and hypopnea which is the cause of pathogenetic disorders. These mechanism consequences impact on hemodynamics and metabolism, increasing the risk of cardiovascular diseases such as heart failure, high blood pressure, and pulmonary hypertension (8). Moreover, OSA may give serious consequences on the mental, motor, and physical development of children because it affects directly on the process of physical and psychological development. It induces cognitive impairment, lack of concentration, decreased learning and memory ability (9).

Currently, the main treatments of OSA in children is adenotonsillectomy. However, this intervention is an invasive method for children with asthma (1). Some recent reported showed that tonsillar tissue from children with OSA may overexpress cysteine leukotriene receptor-1 (CysLT1), which can be treated with anti-inflammatory therapy such as leukotriene receptor antagonists (10, 11). In children with non-severe OSA, this therapy might have the potential efficacy in the treatment of asthmatic children with OSA associated with adenotonsillar hypertrophy (11, 12).

Therefore, the present study was realized to describe the clinical and functional characteristics of OSA in children with asthma and the clinical efficacy of antileukotriene drugs in the treatment of asthma and OSA in these children.

Methods

Subjects

There were 99 patients over 5 years old who were diagnosed and treated with asthma in the Department of Immuno-Allergology, Asthma and Rheumatology of the National Children's Hospital from January 2016 to January 2019. The present study was approved by the Ethics Council in Biomedical Research of Hanoi Medical University within the decision No. 187/HDDD/DHY-HN.

Inclusion criteria

Children having the following criteria were included in the present study: aged >5 years-old, diagnosed with asthma according to GINA and without acute asthma attacks; being able to do the required tests; the agreement and written consent were obtained from patients or their guardians.

Exclusion criteria

Children having one of the following criteria were excluded from the study: having an acute respiratory infection; being unable to perform the laboratory testings; patients with other acute or chronic diseases (heart failure, renal failure, or mental disorders); patients with current treatment of corticosteroids (oral or intranasal); patients with oral antihistamine preparations or nasal decongestants; patients with adenotonsillar hypertrophy.

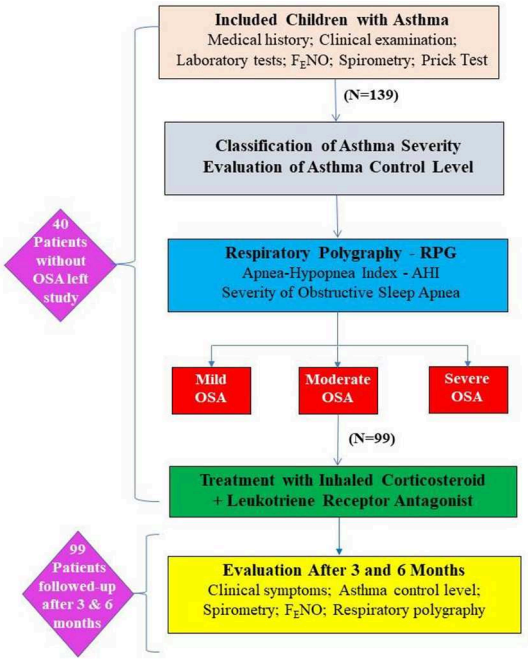

FIGURE 1
Flowchart of the study method. AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; RPG, respiratory polygraphy.

Study design

It was a cross-sectional and cohort study, including asthmatic children >5 years who were followed-up in the Department of Immuno-Allergology, Asthma and Rheumatology of the National Children's Hospital, Hanoi – Vietnam. Asthmatic childrens received clinical examination, biology tests, skin prick-test, lung function testing with spirometry and respiratory polygraphy (Figure 1). They were then classified as mild, moderate or severe OSA based on the apnea – hypopnea index (AHI) and treated with inhaled corticosteroid (ICS) plus leukotrien receptor antagonist (LRA).

Asthma evaluation

The diagnosis of asthma was based on the criteria recommended by Global Initiative for Asthma (GINA) 2015 for children over 5 years old (13). Depending on asthma severity, the study subjects were treated as recommended by GINA (13). The asthma control test (ACT) was used as a self-assessment by the study subjects (≥12 years) or their parents (<12 years). The level of asthma control was defined as recommended by GINA: controlled, partially controlled, and uncontrolled asthma (13).

Lung function testing (LFT)

LFT (*spirometry*) was done by Koko (nSpire Health, Inc., Longmont, CO, USA). The reversibility of forced expiratory volume in one second (FEV_1) was evaluated after using 200 μg of salbutamol for 15 min. The test was positive when there was the increase of FEV_1 ≥12% and >200 mL (14). Measuring exhaled NO concentration was done by Hypair FeNO+ Device (Medisoft; Sorinnes, Belgium) with expiratory air flow of 50, 100, 150, and 350 mL/s. The fractional exhaled nitric oxide (F_ENO) levels were classified as recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) for children (<20 ppb: normal, 20–35 ppb: increased, and >35 ppb: highly increased) (15). The level of alveolar concentration of exhaled NO (C_ANO) <5 ppb was defined as normal (15).

Skin prick test (SPT)

The SPT was done by using Stallergenes Kit (Stallergenes; London, UK), and the negative control was 0.9% saline solution and the positive control was 1 mg/mL of histamine. Six respiratory allergens, including *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), *Blomia tropicalis* (Blo), and hairs and epidermis of dogs, cats, and cockroaches were tested. The SPT was considered positive when the wheal size exceeded the negative control by 3 mm (14).

Respiratory polygraphy (RPG)

RPG was done with Apnea Link device (ResMed; San Diego, California, USA). OSA was defined with RPG by using AHI to classify the severity of OSA in children as recommended: normal (non-OSA): AHI <1/h; mild OSA: 1/h ≤ AHI ≤ 5/h; moderate OSA: 5/h < AHI ≤10/h; severe OSA: AHI >10/h (16).

Data collection

All data related to age, gender, height, weight, BMI, medical and family history of asthma, clinical characteristics, LFT parameters (FEV_1, FVC, FEV_1/FVC, and PEF), exhaled NO (bronchial F_ENO, nasal F_ENO, and CANO), SPT and RPG parameters of the study subjects were collected for statistical analyses.

Statistical analysis

SPSS 22.0 software (IBM Corporation, Armonk, NY, USA) was used to analyse the collected data. Continuous variables were presented as mean ± standard deviation

(SD). Skewness-Kurtosis test was used for evaluating the normal distribution and Kruskal- Wallis test was done for performing the pairwise comparison. The regression analysis was used to measure the correlation between AHI and continuous variables, with the correlation coefficient *R* of Pearson for normal distribution variables and of Spearman for non-normal distribution variables. The Mann–Whitney *U*-test was used to evaluate the correlation between AHI and asthma severity.

Results

Clinical, biological and functional characteristics of study subjects

The results of the present study showed that among 139 asthmatic children there was only 99 patients with OSA were included for analysis. Among these 99 patients, male patients were accounted for 74.7% and its percentage was 2.8 times higher than female (Table 1). The mean age of study patients was 9.26 years (range: 5–15 years old) with the mean BMI of 17.4 kg/m^2. Among these 99 asthmatic patients with OSA, there was 91.9% having the history of allergic conditions; of which, allergic rhinitis was the most common comorbidity (85.86%); 64.7% of them had siblings, parents or grandparents with allergic diseases (Table 1). There was 14.1% of study subjects had been diagnosed with gastroesophageal reflux. Approximately 44.4% of the study subjects had mild asthma, 10.1% with intermittent asthma, 41.41% with moderate asthma and 4.04% had severe asthma (Table 1). Among them, 58.59% of subjects were in uncontrolled asthma, 32.32% were in partially controlled asthma and 9.09% with controlled asthma. There were 61.6% of patients with mild OSA, 25.3% with moderate OSA, and 13.1% with severe OSA (AHI $\geq$10/h). The average AHI index was 3.45 $\pm$ 4.01/h (1–21/h) (Table 1).

The majority of asthmatic children were allergic to house dust mites with 67.7% for *Dp*, 69.7% for *Df*, and 44.4% for *Blomia tropicalis* (Table 1). The mean levels of IgE and the percentage of eosinophils in the study subjects were higher than normal values (Table 1). The mean FEV_1 and peak expiratory flow (PEF) in the study subjects were mildly lower than normal values, while other parameters (FEV_1/FVC and FVC) were in normal range (Table 1). The nasal and bronchial F_ENO were higher than normal values (1,505 $\pm$ 951.8 ppb and 22.1 $\pm$ 20.4 ppb; respectively; Table 1).

Nocturnal and daytime symptoms and odds ratio of OSA in study subjects

The results showed the high percentages of asthmatic children with OSA who had snoring (61.6%), disturbed sleep

TABLE 1 General characteristics of study subjects.

Parameters (N = 99)	Values
Age, years (mean $\pm$ SD)	9.26 $\pm$ 0.19
Female (Male), %	25.3 (74.7)
Height, cm	132.8 $\pm$ 1.13
Weight, kg	31.1 $\pm$ 0.85
BMI, kg/m^2	17.4 $\pm$ 2.8
Allergy status, %	91.9
Eczema,%	34.3
Allergic rhinitis,%	85.8
Conjunctivitis,%	42.4
Drug allergies, %	3.0
Food allergies, %	13.1
Family history of allergy, %	64.7
Gastroesophageal reflux, %	14.1
Asthma severity level	
Intermittent, %	10.1
Mild, %	44.4
Moderate, %	41.4
Severe, %	4.0
Level of asthma control	
Total controlled, %	9.1
Partially controlled, %	32.3
Uncontrolled, %	58.5
ACT Score, mean $\pm$ SD	19.2 $\pm$ 3.4
Peripheral blood count	
White blood cells, number x10^3/mm^3	9.6 $\pm$ 2.9
Neutrophils, %	52.4 $\pm$ 1.5
Lymphocytes, %	33.1 $\pm$ 1.3
Eosinophils, %	6.4 $\pm$ 5.0
CRP mg/L, median (min-max)	3.8 (0 - 58.5)
IgE, UI/L	1,502 $\pm$ 1,300
Skin prick test	
Dp, %	67.7
Df, %	69.7
Blo, %	44.4
Cockroach, %	22.2
Dog hair, %	13.1
Cat hair, %	17.2

(Continued)

TABLE 1 (Continued)

Parameters ($N = 99$)	Values
Lung function testing	
FEV1, % (mean ± SD)	85.1 ± 16.1
FVC, % (mean ± SD)	92.1 ± 15.0
FEV_1/FVC, % (mean ± SD)	92.3 ± 12.6
PEF, % (mean ± SD)	68.9 ± 17.4
Exhaled nitric oxide	
Bronchial F_ENO, ppb (mean ± SD)	22.1 ± 20.4
Nasal F_ENO, ppb (mean ± SD)	1,505.9 ± 951.8
C_ANO, ppb (mean ± SD)	7.4 ± 6.9
AHI, mean ± SD (min-max)	3.45 ± 4.01 (1–21)
Mild, %	61.6
Moderate, %	25.3
Severe, %	13.1

ACT, asthma control test; BMI, body mass index; AHI, apnea-hypopnea index; Blo, Blomia tropicalis; C_ANO, alveolar concentration of nitric oxide; CRP, C reactive protein; Df, Dermatophagoides farinae; Dp, Dermatophagoides pteronyssinus; F_ENO, fractional exhaled nitric oxide; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; PEF, peak expiratory flow; ppb, part per billion.

(76.8%), and complaints with nocturnal sweats (52.5%). Parents also reported other symptoms: difficulty falling asleep (46.5%), difficulty breathing while sleeping (48.5%), frequently awake (38%), enuresis (11.1%) (Table 2). Asthmatic children who had snoring, disturbed sleep, and difficulty falling asleep were significantly higher odds ratio (OR) of OSA than those without these symptoms [OR = 3.75 (1.7–8.23) and P = 0.01; OR = 2.50 (1.1–5.67) and P = 0.028; OR = 2.44 (1.12–5.34) and P = 0.025; respectively; Table 2]. For daytime symptoms, asthmatic children with abnormal behavior had higher risk of OSA [OR = 3.04 (1.09 – 8.53) and P = 0.034; Table 2].

Correlation between asthma parameters, F_ENO, and OSA severity measured by AHI

The results showed that there was no significant correlation between the level of asthma severity and AHI ($P > 0.05$; Figure 2A). There was no significant correlation between FEV_1 and AHI ($P > 0.05$; Figure 2B). There was a significant and weak correlation between BMI and snoring in asthmatic children with OSA (R = 0.189 and P = 0.027). There were also the very weak correlations between bronchial F_ENO and nasal F_ENO with AHI (R = 0.046 and P = 0.001; R = 0.037 and P = 0.002; respectively; Figures 2C, D).

TABLE 2 Frequency and odds ratio of nocturnal and daytime symptoms of OSA in asthmatic children.

Parameters ($N = 99$)	%	Odds ratio value (95% confidence interval)	P
Symptoms at night			
Snoring	61.6	3.75 (1.70–8.23)	0.010
Difficulty for falling asleep	46.5	2.50 (1.10–5.67)	0.028
Difficulty breathing during sleep	48.5	1.41 (0.67–2.98)	0.365
Disturbed sleep	76.8	2.44 (1.12–5.34)	0.025
Frequent awake	38.3	1.45 (0.67–3.20)	0.352
Nocturnal sweating	52.5	1.22 (0.59–2.55)	0.592
Enuresis	11.1	0.88 (0.29–2.70)	0.816
Daytime symptoms			
Abnormal behavior	30.3	3.04 (1.09–8.53)	0.034
Irritable	46.5	1.80 (0.83–3.90)	0.134
Agitated	29.3	1.46 (0.6–3.37)	0.417
Sleepiness	26.3	2.5 (0.89–7.04)	0.085

Modification of clinical and functional parameters related to asthma after treatment

The results showed that after treating with leukotriene receptor antagonists (LRA), the proportion of intermittent asthma increased from 10.1% at inclusion to 38.3% after 3 months and 60% after 6 months, while moderate and severe asthma decreased from 41.5 to 4.0% at inclusion to 6.1 and 0.0% after 6 months, respectively (Figure 3A). On the other hand, the percentage of un-controlled asthma and partial controlled asthma also decreased significantly (58.5 to 4.0% and 32.3 to 28.2%, respectively; Figure 3B). The percentage of totally controlled asthma increased from 9.1 to 35.5% after 3 months and 67.9% after 6 months (Figure 3B). ACT score increased from 19.2 ± 3.4 to 22.6 ± 4.7 points after 3 months and 24.2 ± 5.2 points after 6 months of treatment. The levels of FEV_1, FVC, peak expiratory flow (PEF) and bronchial F_ENO in the study subjects were improved markedly after 3 months and 6 months of treatment (Table 3).

Modification of clinical and functional parameters related to OSA after treatment

The results of the present study showed that the symptoms related to OSA at night including snoring, difficulty falling

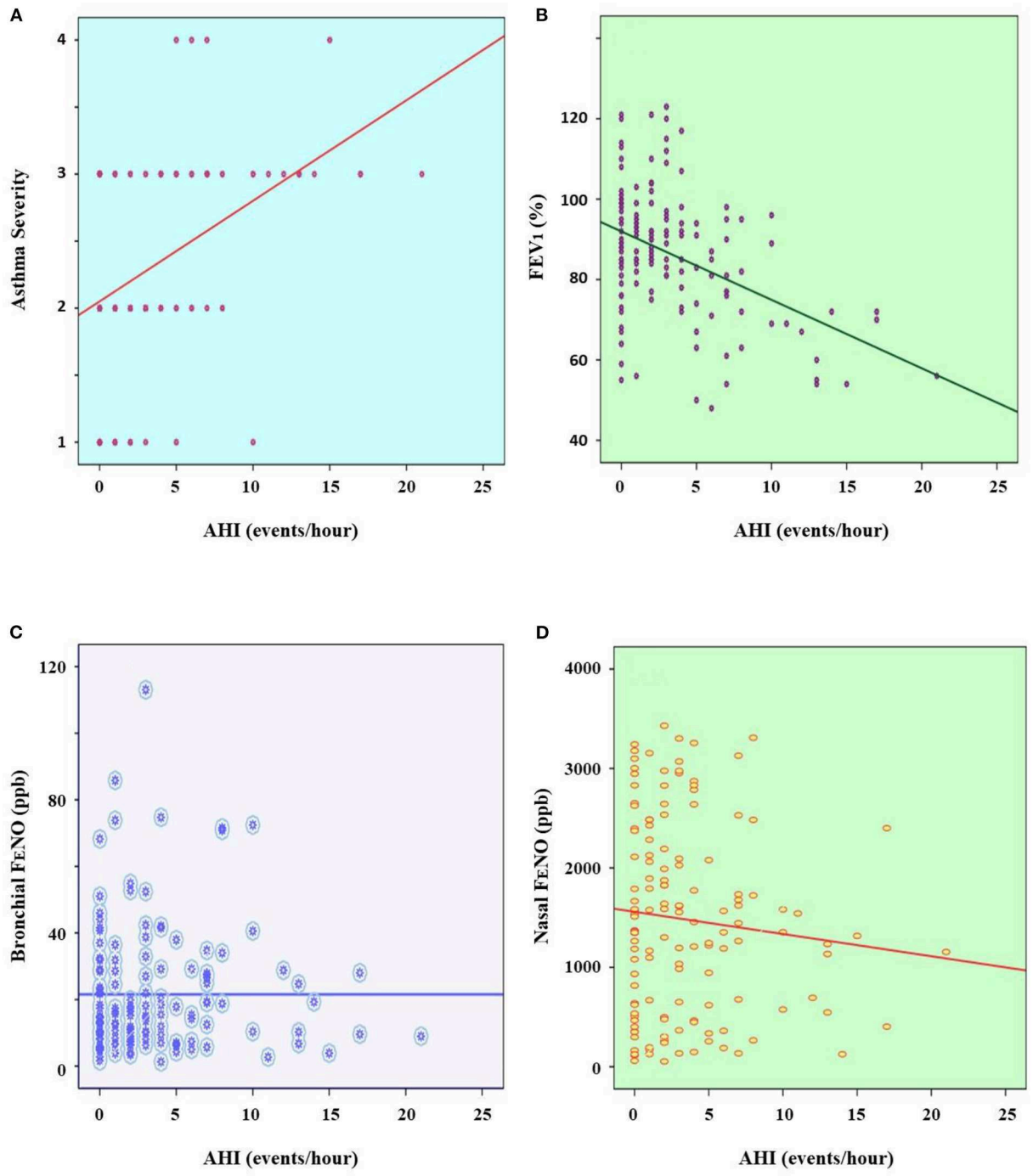

FIGURE 2
Correlation between asthma severity **(A)**, FEV_1 **(B)**, bronchial F_ENO **(C)**, and nasal F_ENO **(D)** with AHI. AHI, apnea-hypopnea index; FEV_1, forced expiratory volume in 1 s; F_ENO, fractional exhaled nitric oxide; ppb, part per billion.

asleep, difficulty breathing during sleep, disturbed sleep, frequent awake, nocturnal sweating, and enuresis were significantly improved after treatment (Table 4). The daytime symptoms due to the consequences of OSA were also improved markedly after treatment (Table 4). Agitation symptom was decreased from 29.3% at inclusion to 0.0% after 6 months of treatment; daytime sleepiness was dropped from 26.3% at inclusion to 3.8% after 6 months of treatment; abnormal

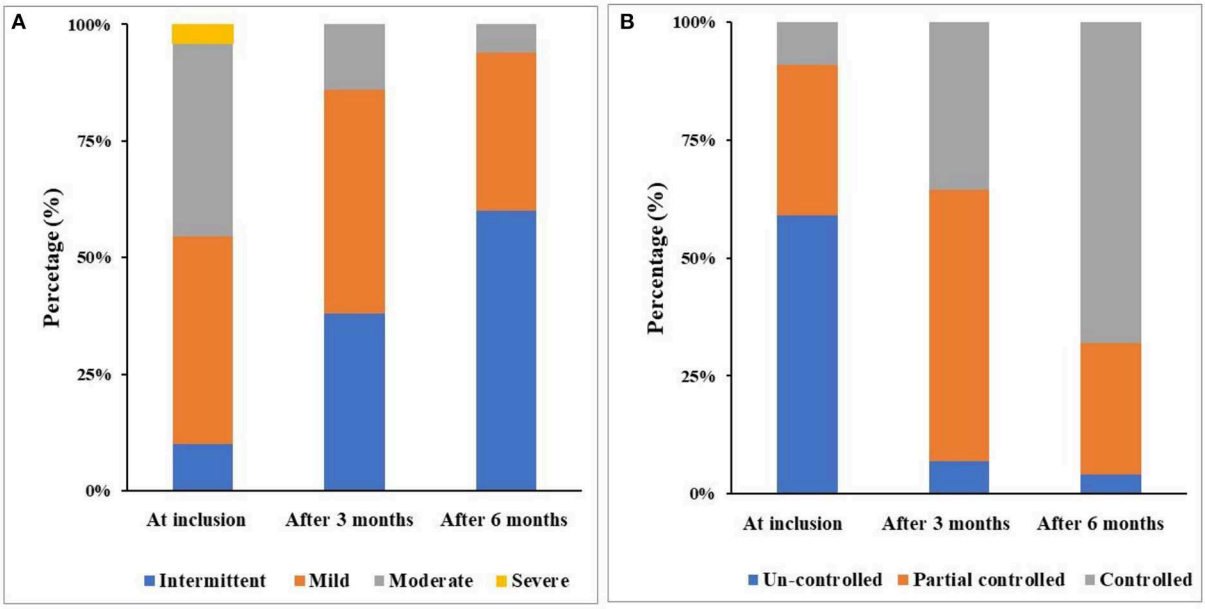

FIGURE 3
Distribution of asthma severity **(A)** and asthma control **(B)** after treatment.

TABLE 3 Modification of respiratory function and bronchial FENO after treatment.

Patient characteristics ($N = 99$)	At inclusion	After 3 months	After 6 months	*P*
FEV1, %	85.1 ± 16.1	94.3 ± 14.5	99.2 ± 16.7	0.032*; 0.004**; 0.067***
FVC, %	92.1 ± 15	99.3 ± 14.6	103.2 ± 12.7	0.058*; 0.037**; 0.076***
FEV1/FVC, %	92.3 ± 12.6	96.3 ± 13.5	96.0 ± 12.8	0.055*; 0.059**; 0.972***
PEF, %	68.9 ± 17.4	78.2 ± 16.3	80.1 ± 17.3	0.021*; 0.016**; 0.122***
Bronchial FENO, ppb	22.1 ± 20.4	15.1 ± 12.5	14.3 ± 11.6	0.019*; 0.014**; 0.233***
ACT score	19.2 ± 3.4	22.6 ± 4.7	24.2 ± 5.2	0.046*; 0.038**; 0.225***

ACT, asthma control test; FENO, fractional exhaled nitric oxide; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; ppb, part per billion. *After 3 months vs. at inclusion; **After 6 months vs. at inclusion; ***After 6 months vs. after 3 months.

behavior was decreased from 30.3% at inclusion to 9.4% after 6 months of treatment (Table 4).

The results demonstrated that the severity of OSA was significantly reduced after 3 months and 6 months of treatment by LRA. The percentage of moderate OSA was decreased from 25.3% at inclusion to 2% after 6 months. The percentage of study subjects with severe OSA was significantly reduced from 13.1 to 0.0% after being treated with LRA. The percentage of study subjects without OSA was significantly increased after being treated with LRA (0.0 vs. 28%) (Figure 4).

Discussion

The results of the present study showed that among 139 children with asthma there was 99 patients with OSA were included in the study (Table 1). Hence, the incidence of OSA in asthmatic children was high, accounting for 71.2% (data not shown). High prevalence of OSA in asthmatic patients may be due to asthma shares the same risk factors for OSA such as allergic rhinitis. This disease increases the risk of upper airway collapse, apnea – hypopnea events, and respiratory efforts to overcome the narrowing of upper airways during sleep (4–7, 17). The average age of the study subjects was 9.3 years with an average BMI of 17.4 kg/m^2, of which male patients accounted for 73.4%, higher than female patients 2.8 times (Table 1). Gender differences in asthma in children have also been better described and understood in recent years (18). In the 1st years of life, boys were at higher risk of asthma than girls with the proportion of asthmatic boys was almost twice of girls (18).

There are some similar clinical manifestations sharing between OSA and asthma during the night such as low quality of sleep, snoring, shortness of breath, intermittent

TABLE 4 Modification of clinical symptoms related OSA after treatment.

Patient characteristics ($N = 99$)	At inclusion % (N)	After 3 months % (N)	After 6 months % (N)	P
Symptoms at night				
Snoring	61.6 (62)	44.4 (44)	6.0 (6)	0.005*; <0.00001**; <0.00001***
Difficulty for falling asleep	46.5 (47)	18.1 (18)	11.1 (11)	<0.001*; <0.001**; 0.079***
Difficulty breathing during sleep	48.5 (48)	5.1 (5)	0.0 (0)	<0.00001*; <0.00001**; <0.00001***
Disturbed sleep	76.8 (76)	73.7 (73)	56.6 (55)	0.310*; <0.001**; <0.003***
Frequent awake	38.3 (38)	9.1 (9)	0.0 (0)	<0.00001*; <0.00001**; 0.001***
Nocturnal sweating	52.5 (52)	18.1 (18)	2.0 (2)	<0.00001*; <0.00001**; <0.0001***
Enuresis	11.1 (11)	0.0 (0)	0.0 (0)	<0.0001*; <0.0001**; N/A***
Daytime symptoms				
Abnormal behavior	30.3 (30)	17.2 (17)	9.4 (9)	0.014*; <0.0001**; 0.046***
Irritable	47.4 (47)	37.3 (37)	26.3 (26)	0.075*; <0.001**; 0.046***
Agitated	29.3 (29)	8.1 (8)	0.0 (0)	<0.0001*; <0.00001**; 0.001***
Sleepiness	26.3 (26)	13.1 (13)	4.1 (4)	0.010*; <0.0001**; 0.011***

*After 3 months vs. at inclusion; **After 6 months vs. at inclusion; ***After 6 months vs. after 3 months. NA, not applicable.

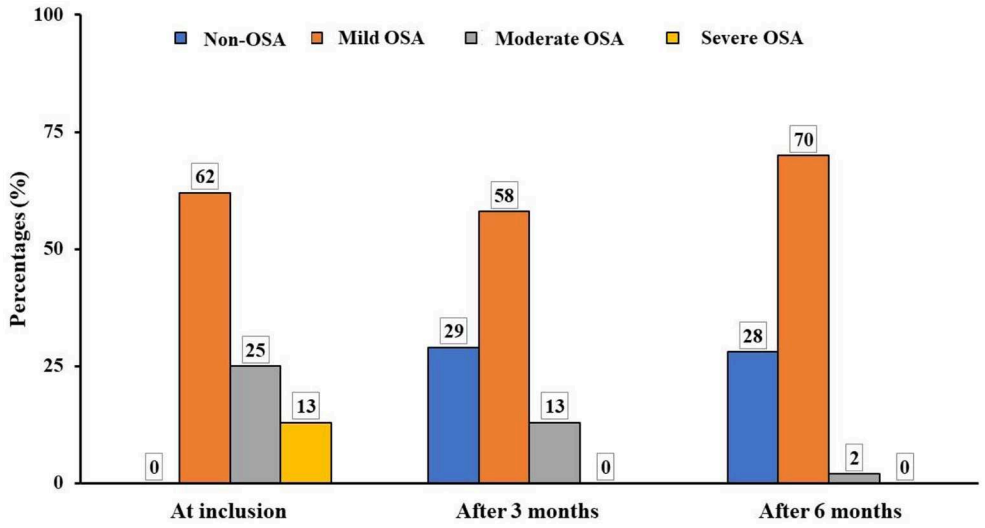

FIGURE 4
Modification of OSA severity after treatment in study subjects. OSA, obstructive sleep apnea.

apnea - hypopnea, frequent wake-up, difficulty falling asleep, sweating, or enuresis (19). In the present study, children with asthma who had nighttime symptoms such as snoring (61.6%), difficulty for falling asleep (45.5%), disturbed sleep (76.8%), and frequent wake-up (34.8%) increased the risk of OSA (Table 2). The present study also showed that there was a significant correlation between BMI and snoring index ($R = 0.189$ and $P = 0.027$; data not shown). Other symptoms such as difficulty of breathing during sleep, frequent wake-up, sweating in children with asthma did not increase the risk of OSA (Table 2). It suggests that a difficulty of breathing during sleep and other symptoms might be related to the characteristics of asthma at night rather than OSA (20).

Children with OSA and without asthma often present with snoring during sleep, shortness of breath, or may not be able to fall in sleep or often wake up (1). It reduces the quality of children' sleep and does not help them to have a refresh after sleep (1). For older children, sleep disturbance might increase the risk of personality and/or behavior disorders, physical or mental development delay that may affect their learning, memorizing and health issues (8). In the present study, the results of daytime symptoms of asthmatic children with OSA showed that 46.5% of them were irritable, 30.3% had abnormal behavior, 29.3% were agitated and 26.3% had daytime sleepiness (Table 2). This proportion was relatively high and suggests that it is very harmful if the patients did not have the proper treatment. Moreover, the present study revealed that most asthma patients had a atopy and 85.86% of them had allergic rhinitis (Table 1). Previous study reported that nearly 80% of asthmatic patients with allergic rhinitis was associated with an increased risk of OSA (21).

In children without asthma, the prevalence of OSA has been varied from 1 to 5% and it may be occurred in all ages within the highest incidence in 2–8 years (8–12%) (1–3). In comparison with children without asthma, the higher prevalence of OSA in asthmatic children suggests that this high prevalence of comorbidity could require a special attention because it can make asthma more difficult to control (1, 13). In patients with asthma, OSA plays a role as a contributor for aggravating asthma because the upper airway obstruction due to OSA in nocturnal asthmatic patients might be associated with sleep disturbances and daytime sleepiness (19, 20). However, the correlation between asthmatic subjects with OSA and asthma severity, treatment adherence, and asthma control remains controversial (22, 23). In children, based on the result of the recent systematic review, Sánchez et al. revealed that children with asthma were more likely to develop habitual snoring and OSA, and children with sleep disordered breathing were more likely to develop asthma (22). This result is similar with our previous study (17).

The present study could not find out the significant correlation between FEV_1 and AHI index (Figure 2B). It might suggest that the degree of bronchial obstruction is not related to the severity of OSA in asthmatic children with OSA. Therefore, the use of spirometry alone is not useful for screening patients with OSA. This feature might be due to the pathogenesis of OSA is mainly related to the obstruction of upper airways (1, 3). The present study also demonstrated that asthmatic patients with OSA had the high levels of exhaled NO (bronchial and nasal F_ENO and C_ANO) for children (Table 1). Interestingly, there were only the weak significant correlations between bronchial and nasal F_ENO with AHI (Figures 2C, D). Although the level of exhaled NO might be increased in adult with OSA (24), in children with asthma, the high level of exhaled NO has been considered as a marker of allergic inflammation due to eosinophilia that has not been well controlled by ICS and requires increased ICS dose as suggested by our previous study (14, 25). However, if clinical symptoms of asthma are well-controlled and confirmed by ACT scores, it may suggest that high level of F_ENO in asthmatic patients with OSA might be contributed by airway inflammation due to oxidative stress (25).

The present study also demonstrated that after 6 months of treatment, the percentage of intermittent asthma patients increased significantly compared to at inclusion; notably, the percentage of moderate asthmatic patients was decreased significantly (Figure 3A). Especially, after 6 months of treatment, there was no patient with severe asthma. This result suggests that the combination of ICS and LRA in asthmatic children with OSA could improve asthma severity as recommended by GINA (26). In addition, the percentage of uncontrolled asthma was also decreased after combined treatment with ICS and LRA; inversely, the percentage of well controlled asthma was increased significantly after 3 months and 6 months of treatment (Figure 3B). Consequently, the mean ACT scores were significantly increased after treatment (Table 2).

In the present study, the improvement of clinical symptoms of asthma was also confirmed by the modification of respiratory parameters, such as low FEV_1 and PEF at inclusion compared with those higher after 3 months and 6 months of treatment ($P < 0.05$; Table 3). These results are consistent with Anandi's study on 32 asthmatic children aged 6–12 years old, with improved clinical symptoms, increased FEV_1 and FVC values after 3 months of treatment, and PEF was increased significantly after 6 months of treatment (27). In the present study, the mean levels of bronchial F_ENO of asthmatic children measured after 3 months and 6 months of treatment were lower than that at inclusion ($P < 0.05$; Table 3). Thus, bronchial $F_ENO < 20$ ppb has been recommended as the target of controlled asthma monitoring (16).

Obviously, the results of the present study showed that after 6 months of treatment with ICS and LRA there was an significant improvement of OSA symptoms in study subjects, especially for nocturnal symptoms, such as snoring and difficulty for falling asleep which were improved after 3 months and 6 months of treatment (Table 4). Other symptoms at night were also improved remarkably, including difficulty of breathing during sleep and frequent awake (Table 4). Other daytime symptoms were also improved significantly after 3 months and 6 months of treatment. For instance, abnormal behavior and daytime sleepiness were decreased sharply after 6 months (Table 4). This result is similar with previous published studies (10, 12). In addition, in the present study, the results of RPG confirmed OSA severity was decreased significantly after 3 months and improved after 6 months of treatment with ICS and LRA for asthma (Figure 4). Definitely, the percentage of children with moderate or severe OSA was significantly reduced after the combined treatment; it was similar to previous studies (1, 28).

The present study showed that after giving the treatment with LRA, there was no case with side effects was detected and required the treatment discontinuation. Hence, this treatment could be considered as an effective therapy for improving both clinical symptoms and RPG (10, 12). The results of the present study after 6 months confirmed the treatment of asthma with ICS in combination with LRA had both effective role in the asthma control and in the improvement of the symptoms and severity of OSA. Finally, the main limitations of the present study have been related to the limited number of study population, the short duration for patients' follow-up (only 6 months), and the lack of controlled asthmatic group without OSA. Therefore, the long-term follow-up with large scale study population and randomized controlled study could be necessary for evaluating the first choice of ICS combined with LRA in the treatment of asthmatic children with suggested OSA symptoms for a personalized therapy in the future of asthma management.

Conclusion

OSA is a common comorbidity in children with asthma. Asthmatic children with OSA usually have the symptoms at night and its consequences during the day. The presence of snoring, high exhaled NO level, and dyspnea during sleep in asthmatic children may be associated with a higher risk of OSA. The treatment with leukotriene receptor antagonists, in combination with inhaled corticosteroids according to GINA recommendations, for children with asthma can improve both asthma control and symptoms of OSA in asthmatic patients with comorbid OSA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Council in Biomedical Research of Hanoi Medical University within the Decision No. 187/HDDD/DHY-HN. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SD-Q, YN-H, LN-N-Q, MN-T-P, HN-T-B, HL-T-M, and TN-T-D: conceptualization, validation, and writing—original draft preparation. SD-Q, YN-H, LN-N-Q, and TN-T-D: methodology and writing—review and editing. SD-Q, YN-H, and LN-N-Q: software. SD-Q, YN-H, LN-N-Q, HL-T-M, and TN-T-D: formal analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer TNNP declared a shared secondary affiliation with the author SD-Q to the handling editor at the time of review.

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Clinical-functional characteristics of children with asthma and obstructive sleep apnea overlap associated with attention deficit hyperactivity disorder: A cross-sectional study

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Background: Asthma and obstructive sleep apnea (OSA) are common chronic respiratory disorders in children. The relationship between asthma and OSA is bidirectional; these conditions share multiple epidemiological risk factors. Untreated OSA may cause attention deficit hyperactivity disorder (ADHD) symptoms. This study aimed to assess the prevalence of ADHD in asthmatic children with OSA and the link between asthma control and lung function of children with asthma and OSA.

Methods: A total of 96 children aged 6–15 years diagnosed with asthma, according to the Global Initiative for Asthma (GINA) 2020, were enrolled in this study. All demographic data, including age, gender, body mass index, asthma control status, therapy, the Vanderbilt ADHD Diagnostic Parent Rating Scale, lung function, and exhaled nitric oxide, were collected. In addition, home respiratory polygraphy was used to identify OSA in study subjects.

Results: A total of 96 patients (8.4 ± 2.4 years) were included in the present study. OSA was identified in 60.4% of asthmatic children with a mean apnea-hypopnea index (AHI) of 3.5 ± 3.0 event/h. The inattentive ADHD subtype was significantly lower in the non-OSA asthmatic group than in the OSA asthmatic group (7.9 vs. 34.5%, $p < 0.05$). ADHD had a higher probability of presence (OR: 3.355; 95% CI: 1.271–8.859; $p < 0.05$) in the OSA group (AHI >1 event/h). Children with poorly controlled asthma had a significantly high risk of OSA (83.0 vs. 17.0%, $p < 0.001$) than children with well-controlled asthma. Allergic rhinitis increased the odds of having OSA in patients with asthma [OR: 8.217 (95% CI: 3.216–20.996); $p < 0.05$].

Conclusion: The prevalence of OSA is increased among poorly controlled asthma. ADHD may have a higher prevalence in children with OSA. Therefore, prompt diagnosis of OSA will lead to an accurate asthma control strategy in patients with asthma.

KEYWORDS

asthmatic children, asthma control, respiratory polygraphy, OSA, ADHD, AHI

Introduction

Asthma is one most common major non-communicable diseases in children (1). The prevalence of current wheeze was still high in children and adolescents in low-income countries and increased in lower-middle-income countries (1). Despite advances in asthma control, the asthma-related mortality rate remains high in lower-middle-income countries (2). There is still much work to be done to improve patient education, approach diagnostic tools, and personalize asthma management.

Obstructive sleep apnea (OSA) is defined as repetitive episodes of complete or partial upper airway obstruction during sleep (3). OSA occurs in 1–3% of children (4), especially in the early school and pre-school age, with a peak at the age of 2–8 years and declines in frequency of age (3, 4). The gold-standard diagnostic method for OSA is overnight polysomnography (PSG) or respiratory polygraphy (RPG), with an apnea-hypopnea index (AHI) $\geq$ 1 event/h associated with the presence of signs and symptoms of OSA (3). Risk factors of childhood OSA are hypertrophy of tonsils, adenoids, and obesity (3, 4).

For the last few decades, several studies have been carried out on the interaction between OSA and other lower airway diseases, especially asthma, in terms of prevalence, pathophysiology, and treatment (5–8). A randomized sample survey of 1,234 children aged 6–14 years in Belgium revealed a 2.0-fold increase in OSA symptoms among children with wheezing (4, 6). However, these two diseases' pathophysiology is likely to overlap because they are all affected by inflammation, neurologic factor, and morphologic manifestation such as obesity (7, 9). Snoring and noisy breathing have been considered the characteristics of OSA in children, but they are also common complaints in asthmatic children (9, 10). On the other hand, airway inflammation and resistance in nocturnal asthma reduced airway flows while sleeping, causing interrupted sleep and/or poor quality of sleep (11). Inversely, systemic corticosteroids for unstable asthma treatment may increase the risk of OSA in children who had both conditions (9). In contrast, OSA plays a role as a contributing mechanism to worsen asthma (11). Ramagopal et al. pointed out that the AHI score was significantly higher than the control in African-American children with poorly controlled asthmatic (12).

In children, OSA might cause intermittent nocturnal hypoxia due to apnea and hypopnea episodes (3), induce cardiovascular disease and metabolic syndrome (3), and lead to increased morbidities and physical development in children with OSA (3, 13). Moreover, Beebe and Gozal suggested that OSA-induced hypoxia and sleep disturbances negatively impact the recovery benefits of sleep (14), cause cellular and chemical imbalance leading to prefrontal cortical dysfunction, and increase neurobehavioral disorders, which can express as overactivity and impulsivity in children (14). Preliminary evidence also suggests that OSA may influence or contribute to attention deficit and hyperactivity disorder (ADHD) symptoms in untreated patients (10, 13). Some research had shown that ADHD and OSA have overlap in diagnosis (13, 15), for example, attention deficit was reported in 95% of pediatric patients with OSA (13), while other research showed a significant link between ADHD and childhood asthma (15). ADHD, OSA, and asthma had a complex relationship, with each syndrome influenced the symptoms of the others (13–15).

This study aimed to examine the clinical characteristics and lung function of asthmatic children with OSA, the prevalence of ADHD among these patients, and the relationship between ADHD and OSA in children with asthma.

Methods

Subjects

Sample size calculation

Based on the study by Nguyen-Hoang et al. (16), which showed the prevalence of OSA in asthmatic children was 65.9%, the estimated cohort size was done using the following equation:

$$n = Z^2(1-\alpha/2)\times\frac{p(1-p)}{\Delta^2}$$

(n = number of subjects; p = expected proportion = 0.65; α = type I error = 0.05; two-sided 95% Confidence Interval, Z = 1.96).

Δ = distance from proportion to limit = 0.1.

$$n = 1.96^2 \times \frac{0.65(1 - 0.65)}{0.1^2} = 87$$

Approximately 10% of the sample size was added for the possible drop-off and attrition during the study; the sample size was 96.

The convenient sample of 96 children aged 6–15 years visited the Asthma Outpatient Unit of the Immunology-Allergy-Rheumatology department in the National Children's Hospital, Vietnam, for asthma diagnosis and follow-up from 1 August 2020 to 30 June 2021 and were enrolled in this study. Since family medicine is not common in Vietnam, parents could make an appointment directly in the asthma clinic. Asthmatic outpatients had been examined by physicians from the Immunology-Allergy-Rheumatology department. The Global Initiative for Asthma (GINA) guideline for children aged above 5 years had been used for the diagnosis and management of asthma in this study (17).

Inclusion criteria

Children aged between 6 and 15 years who were diagnosed with asthma according to the Global Initiatives for Asthma (GINA) 2020 for children aged above 5 years (17) were included in the study.

Exclusion criteria

The exclusion criteria were as follows: patient diagnosed with other significant chronic or acute diseases, patient with facial structure malformation, or patient with mental disorders, which caused subjects to be unable to perform spirometry and respiratory polygraphy.

Methods

Study design

It was a cross-sectional and prospective study. The algorithm of the study had been provided in Figure 1.

Asthma control selection criteria

The GINA asthma control assessment consists of four questions about asthma symptoms and therapy in the past 4 weeks including frequent use of rescue medications, shortness of breath, nocturnal awakening, and daily activity limitations (17). Based on these symptoms, GINA defined asthma as "well-controlled," "partly controlled," or "uncontrolled" asthma. A "poorly controlled" asthma group included "partly controlled" and "uncontrolled" asthmatic children.

The present study used the Asthma Control Test (ACT) for children 12 years and older to measure the level of asthma control (18). The ACT questionnaire evaluates asthma symptoms in the previous 4 weeks. ACT score $\geq$20 characterizes "controlled asthma," an ACT score from 16 to 19 indicates "partly controlled asthma," and an ACT score $\leq$15 indicates "poorly controlled asthma" (18). In the present study, patients with an ACT score $<$ 20 were considered "poorly controlled asthma." The Vietnamese version of ACT was validated in 2012 (19).

For children older than 4 and younger than 12 years, this study used the c-ACT Test (20). The c-ACT is combined with two parts; the first part has four components and was answered by the child (20). The range of the answers from the first part varied from 0 to 3. The parent or guardian answered the second part with three other components ranging from 0 to 5 (20). The total score of the c-ACT was the sum of all responses, ranging from the value 0 to 27 (20). The value of $<$ 20 was demonstrated as "uncontrolled asthma" (20).

The present study also included information about asthma treatment according to GINA guidelines (17). The medications used by patients with asthma in the present study: inhaled corticosteroids (ICS), ICS-LABA (long-acting beta$_2$-agonist), and leukotriene receptor antagonists (LTRA).

Anthropometry

Children's weight was measured with a calibrated scale to the nearest 0.1 kg, and height was measured with a stadiometer to 0.1 cm (Medisol, Vietnam). The body mass index (BMI) was calculated, and the BMI z-score was computed using Baylor college of medicine Age-Based Pediatric Growth Reference Charts (https://www.bcm.edu/bodycomplab/BMIapp/BMI-calculator-kids.html) (21). The patients were classified as underweight/normal weight with z-scores between -2 and $+0.99$, overweight from 1 to 1.99, obese from 2 to 2.99, and very obese $\geq$3 (22).

Lung function testing

The lung function testing (spirometry) was carried out by using Jaeger Vyntus^{TM} IOS (CareFusion, Germany). The spirometry provided the values of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and the ratio of FEV_1 to FVC, which were adjusted according to sex, age, and ethnicity (17). According to the GINA guidelines, the FEV_1/FVC ratio cut-off of normality was 90% in children (17).

The reversibility of forced expiratory volume in 1 s (FEV_1) was evaluated after using 200 μg of salbutamol for 15 min. The test was positive when there was an increase in FEV_1 $\geq$12% and $>$200 ml (17).

Measuring exhaled NO

The fractional exhaled nitric oxide (FENO) level was measured using Hypair FeNO+ Device (Medisoft; Sorinnes, Belgium) with expiratory airflow of 50, 100, 150, and 350 ml/s.

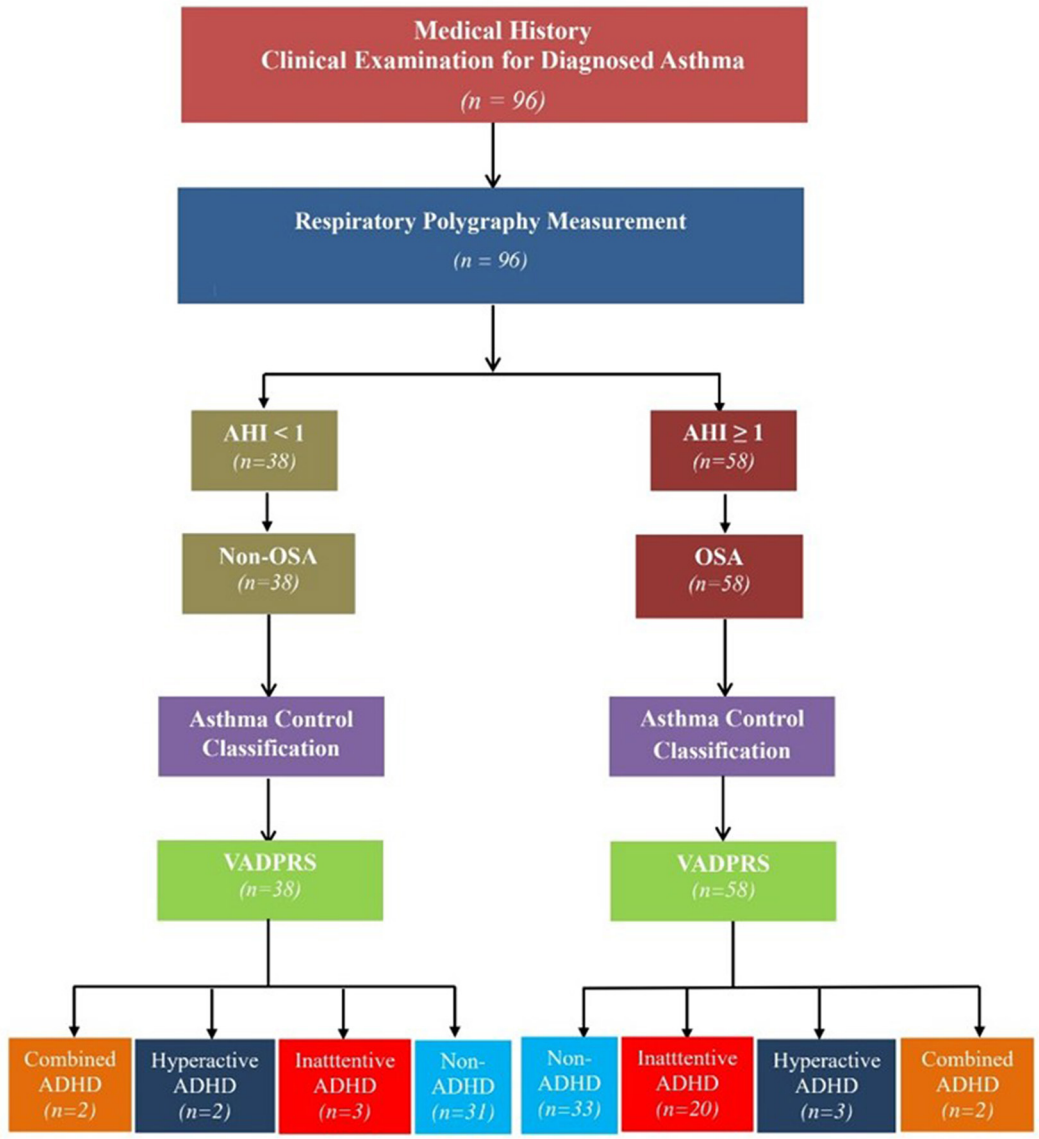

FIGURE 1
Flowchart of the study procedure. ADHD, attention deficit and hyperactivity disorder; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; VADPRS, Vanderbilt's ADHD Diagnostic Parent Rating Scale.

FENO concentrations were classified following the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendation for children: <20 ppb: normal; 20–35 ppb: increased; and >35 ppb: highly enriched (23).

Home respiratory polygraphy

The home respiratory polygraphy system used in the study is the Apnea Link^{TM} Plus (Resmed®, Australia). The ApneaLink^{TM} Plus could record nasal airflow, snoring, respiratory effort, blood oxygen saturation, and heart rate by nasal cannula, pulse oximetry, and thoracic chest belt.

Parents will be provided careful instruction on how to operate the device and to monitor the child; they had also required to perform several trials before using it at home by themselves. When the device had been returned on the following day, trained physicians who were members of the study board would transfer the raw data files to a computer and score automatically by Apnea Link plus application. A home respiratory polygraphy recording will be deemed valid if the recording duration is $\geq$ 5 h. Sections with artifacts or poor

signals will be excluded from the analysis. If a home respiratory polygraphy is not valid, it will be repeated within the next 7 days.

OSA criteria

For all children < 18 years of age, the American Academy of Sleep Medicine defined pediatric OSA with polygraphy by using the apnea-hypopnea index (AHI) ≥ 1 event/h (24). The severity of OSA was classified as recommending: mild OSA: 1 event/h < AHI ≤ 5 event/h; moderate OSA: 5 event/h < AHI ≤ 10 event/h; severe OSA: AHI > 10 event/h (3, 24).

Parent-reported ADHD measure

Vanderbilt's ADHD Diagnostic Parent Rating Scale (VADPRS) was chosen to measure behavioral problems in the present study (25). The VADPRS is a parent-reported scale including 55 questions, including all 18 of the DSM-IV criteria for ADHD (25). Each question is put a value on a 4-point scale that describes the frequency of each ADHD symptom (0 = never, 1 = occasionally, 2 = often, and 3 = very often) (25). Besides, the VADPRS includes oppositional defiant disorder (8 items), conduct disorder (14 items), and anxiety/depression (7 items) screening scales (25). Finally, the VADPRS includes performance items that assess functional impairment rated on a 5-point scale (1 = excellent performance and 5 = problematic performance) across academic and social domains (25).

The three subtypes of ADHD based on the score include:

- Predominately Inattentive Subtype: If a child has six or more "Often" or "Very Often" on items from 1 to 9 and less than six for items 10–18, combined with a performance problem (scores of 1 or 2) on questions 48–55.
- Predominately Hyperactive/Impulsive Subtype: If a child has six or more "Often" or "Very Often" on items 10 through 18 and less than six for items 1–9, plus a performance problem (scores of 1 or 2) on questions 48–55.
- Combined Subtype: If a child meets the criteria for both inattentive and hyperactive/impulsive subtypes.

Previous studies have suggested a moderately strong sensitivity of 80% and specificity of 75% for the VADPRS-detecting ADHD in children (26).

Data collection

All data of the study subjects including age, gender, BMI score, allergy history, family history, clinical characteristics, measures of spirometry, exhaled NO, therapy, Vanderbilt's ADHD Diagnostic Parent Rating Scale, and respiratory polygraphy parameters were collected and analyzed statistically.

Ethical approval

The study was approved by the Hanoi Medical University Institutional Ethical Review Board (502/GCN-HDDDNCYSH-DHYHN) and followed the 1964 Declaration of Helsinki and its later amendments. Informed consent was required from all participants in the study.

Statistical analysis

IBM SPSS Statistic 20 software (IBM Corporation, Armonk, NY, USA) has been used to calculate and analyze the collected data. Qualitative data were presented as percentages and analyzed with the chi-squared test. Continuous variables were shown as mean ± standard deviation (SD) and compared with *t*-test between 2 groups and a 1-way analysis of variance among groups, followed by paired comparison with the least-significant difference test. Univariate analysis of associated factors for high-risk OSA in asthma children was performed. All variables with $P < 0.25$ on univariate analysis were included in the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. A value of $p < 0$ 0.05 was considered statistically significant.

Results

Descriptive analysis of clinical features of asthma and OSA

During the study period, 96 children with asthma met the inclusion criteria and were enrolled in this study. Their demographic characteristic, comorbidity disease, therapy, and lung function test are shown in Table 1. The mean age was 8.4 ± 2.4 years (6–15 years), including 60.4% of male and 39.6% of female children. Only 10.4% of a subject were overweight or obese (BMI z-scores >1). Approximately 62.5% of the study subjects had a history of allergic rhinitis. Respiratory polygraphy revealed the presence of OSA (AHI> 1 event/h) in 60.4% of study subjects (58 patients) (Table 1). In the present study, 32 patients reported the symptoms of ADHD (33.3%; Table 1).

Among 58 asthmatic children with OSA (60.4%), 36.5% were mild OSA (AHI= 1–4 events/h), 15.6% were moderate OSA (AHI = 5–9 events/h), and 8.3% were classified as severe OSA (AHI ≥ 10 event/h). The average AHI index was 3.45 ± 3.01 event/h (Table 2).

Prevalence of OSA as comorbidity, relationship with asthma control, and other risk factors

The differences between asthmatic children with OSA and those without OSA are shown in Table 2. Children

TABLE 1 Clinical and functional characteristics of study subjects.

Characteristics ($n = 96$)	Mean
Age (years)	8.4 ± 2.4
Gender (% male)	58 (60.4%)
BMI (kg/m^2)	17.1 ± 2.2
BMI z-scores >1, *n* (%)	10 (10.4)
ACT score	20.7 ± 3.7
Asthma control, *n* (%)	
Well-controlled	49 (51.0)
Partly or uncontrolled	47 (49.0)
Therapy, *n* (%)	
ICS, *n* (%)	67 (69.8)
ICS-LABA, *n* (%)	15 (15.6)
Montelukast, *n* (%)	72 (75.0)
Allergic rhinitis, *n* (%)	60 (62.5)
ADHD, *n* (%)	32 (33.3)
FEV1 (%pred)	86.1 ± 16.1
FVC (% pred)	92.6 ± 15.1
FEV1/FVC (%)	93.1 ± 11.5
PEF (% pred)	69.1 ± 16.2
Bronchial FENO (ppb)	21.0 ± 12.9
Respiratory polygraphy	
AHI ≤ 1/h, *n* (%)	38 (39.6)
1< AHI ≤ 4/h, *n* (%)	35 (36.5)
5< AHI ≤ 9/h, *n* (%)	15 (15.6)
AHI ≥ 10/h, *n* (%)	8 (8.3)

ACT, asthma control test; AHI, apnea-hypopnea index; BMI, body mass index; FENO, fractional exhaled nitric oxide; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; ppb, part per billion.

with respiratory polygraphy evidence of OSA were overall anthropometrically similar to those without OSA. However, the frequency of reported symptoms of allergic rhinitis in the asthmatic children with the OSA group was significantly higher than those without OSA (81.0 vs. 34.2%; $p < 0.05$) (Table 2).

A significantly higher prevalence of OSA was found among the poorly controlled asthma group than the well-controlled asthma group (83.0 vs. 17.0%, $p < 0.001$). In addition, the mean value of ACT score in non-OSA was statistically significantly lower than the OSA group (18.2 ± 3.2 vs. 23.8 ± 3.5, $p < 0.05$), reporting a correlation between asthma control and OSA.

Clinical and functional characteristics of asthmatic children with OSA classified by asthma control status

Among those who had OSA, age was associated with a well-controlled asthma status (9.22 ± 2.31 vs. 7.28 ± 3.15, p < 0.05) (Table 3). In addition, children with well-controlled asthma had lower bronchial FENO (18.65 ± 16.75 vs. 33.24 ± 13.21, $p < 0.05$) and higher ACT scores (24.89 ± 5.47 vs. 19.89 ± 4.34, $p < 0.05$) than children with poorly controlled asthma (Table 3). Children with well-controlled asthma also had lower AHI scores than the children with poorly controlled asthma (1.79 ± 1.01 vs. 4.85 ± 1.87, $p < 0.05$).

Odds ratio of OSA for the study subjects

The OR of OSA in children with asthma was evaluated using multivariate logistic regression (Table 4 and Figure 2). The prevalence of OSA increased in the group of asthmatic children with allergic rhinitis (OR: 8.217; 95% CI: 3.216–20.996; $p < 0.05$). Gender, obesity, FEV_1, and asthma control were not associated with the risk of OSA in subjects with asthma.

Prevalence of ADHD and association with OSA comorbidity

Parent-reported symptoms of ADHD by the VADPRS are given in Figure 3. The frequency of parent-reported symptoms of ADHD in asthmatic children with OSA was significantly higher than in those without OSA (43.2 vs. 18.5%, $p < 0.05$). Among asthmatic patients with OSA, 34.5% had a symptom of Inattentive ADHD, which was significantly higher than the non-OSA group (34.5 vs. 7.9%, $p < 0.05$). There were no significant differences between the OSA and non-OSA groups for the prevalence of hyperactive/impulsive ADHD or other behavioral problems.

There were no noticeable differences in age, gender, BMI score, allergic rhinitis, and asthma control between the OSA + ADHD and OSA without ADHD groups (Table 5). However, OSA + ADHD group had significantly higher AHI scores ($p < 0.05$) and marked lower SaO_2 ($p < 0.05$) as compared with the OSA group.

Odds ratio of ADHD for the study subjects

The OR for ADHD in study subjects was analyzed using logistic regression (Table 6 and Figure 4). The result showed that the prevalence of ADHD increased in the subject with OSA (OR: 3.355; 95% CI: 1.271–8.859; $p < 0.05$). However, asthma control, allergic rhinitis, and obesity were not associated with the prevalence of ADHD.

Discussion

This present study emphasizes that asthmatic patients had a high prevalence of OSA as compared with the maximal estimated prevalence of OSA in a non-asthmatic population (60.4 vs. 4.0%, $p < 0.01$) (3, 4). The diagnosis of OSA in this

TABLE 2 Demographic characteristics and asthma control levels of the study subjects classified by OSA.

Characteristics	OSA (+)	OSA (-)	*p*-Value
n	58	38	
Age (years)	8.5 ± 1.5	8.3 ± 2.2	0.478
Male (female), ratio	38/20 (1.9)	20/18 (1.1)	0.286
Allergic rhinitis (*n*, %)	47 (81.0)	13 (34.2)	0.001
BMI score	17.2±3.0	17.4±2.9	0.735
BMI z-scores >1(*n*, %)	7 (12.1)	3 (7.9)	0.614
ADHD (*n*, %)	25 (43.1)	7 (18.5)	0.015
FEV1 (%pred)	75.2 ±16.6	82.6 ± 15.1	0.544
FEV1/FVC (%pred)	64.7 ± 19.0	68.7 ± 11.8	0.537
PEF (%pred)	62.2 ± 11.4	69.2 ± 16.3	0.812
Bronchial FENO, ppb	21.6 ± 12.0	14.2 ± 11.6	0.03
Asthma (*n*, %)			
Well-controlled	19 (38.8)	30 (61.2)	
Partly or uncontrolled	39 (83.0)	08 (17.0)	0.001
Therapy (*n*, %)			
ICS (*n*, %)	40 (69.0)	27 (71.0)	0.695
ICS-LABA (*n*, %)	10 (17.2)	5 (13.2)	0.842
Montelukast (*n*, %)	45 (77.6)	27 (71.1)	0.365
ACT-score	18.2 ± 3.2	23.8 ± 3.5	0.007
Respiratory polygraphy			
AHI (mean)	3.5 ± 3.0	0.5 ± 0.2	
Lowest oxygen saturation, %	82.7 ± 24.1	84.3 ± 28.2	
1<AHI ≤ 5/h, *n* (%)	35 (36.5	-	
5<AHI ≤ 10/h, *n* (%)	15 (15.6)	-	
AHI > 10/h, *n* (%)	8 (8.3)	-	

ACT, asthma control test; AHI, apnea-hypopnea index; BMI, body mass index; FENO, fractional exhaled nitric oxide; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; ppb, part per billion.

study is based on AHI measurement following the American Academy of Sleep Medicine guideline (3, 24). The mean AHI of study subjects measured by respiratory polygraphy is 3.5 ± 3.0 events/hour and is considered mild OSA. Several studies have shown that OSA is common in the asthmatic population (3, 5, 6, 15). In one study, Kheirandish-Gozal et al., subjected 92 poorly controlled asthma children between 3 and 10 years to overnight polysomnography (2). OSA was present in 58 patients, with a prevalence of 63% (3). In another study, the majority of OSA in Vietnamese asthmatic children is 65.9% (16).

Many studies have reported the bidirectional connection between OSA and asthma, including incidence, risk factors, pathophysiology, and treatment (5, 7, 8). In the present study, we found that the coexistence of OSA (diagnosed based on respiratory polygraphy) was significantly more frequent in poorly controlled asthma children than in the well-controlled asthma group (83.0 vs. 17.0%, $p < 0.001$). It means that poorly controlled asthma was able to be a risk factor for OSA in children. These findings are similar to other previous studies (5, 27). In a recent study of 203 children with asthma aged 3–16 years (27), there was a significantly higher prevalence of OSA in the poorly controlled asthma group than in children with well-controlled asthma (34.2 vs. 13.97%, $p < 0.01$) (27). Another large multicentric cross-sectional study was conducted to investigate the frequency of asthma and sleep-disordered breathing among school-aged children in China (5). The authors demonstrated that sleep-disordered breathing, such as chronic snoring (OR = 1.28, 95%CI: 1.01–1.62), and OSA (OR = 1.92, 95%CI: 1.34–2.76) were significantly associated with asthma, after adjusting for potential confounding factors (5).

Studies in children with OSA have investigated the association of OSA with systemic inflammation and localized

TABLE 3 Characteristics of the asthmatic group with OSA classified by asthma control status.

Characteristics	Well-controlled asthma	Partly or uncontrolled asthma (-)	*p*-Value
N	23	35	
Age (years)	9.22 ± 2.31	7.28 ± 3.15	0.012
Male (female), ratio	14/9 (1.6)	24/11 (2.2)	0.409
Allergic rhinitis (*N*, %)	17 (73.91)	30 (85.71)	0.532
BMI score	16.92 ± 4.87	17.34 ± 3.95	0.127
Obesity (*N*, %)	4 (17.39%)	3 (8.57)	0.544
FEV1 (%pred)	81.51 ± 19.18	77.56 ± 20.41	0.337
FEV1/FVC (%pred)	85.48 ± 21.55	80.55 ± 19.0	0.134
PEF (%pred)	77.23 ± 22.14	72.57 ± 25.67	0.708
Bronchial FENO, ppb	18.65 ± 16.75	33.24 ± 13.21	0.0075
ACT-score	19.89 ± 4.34	24.89 ± 5.47	0.01
AHI score	1.79 ± 1.01	4.85 ± 1.87	0.022

ACT, asthma control test; AHI, apnea-hypopnea index; BMI, body mass index; FENO, fractional exhaled nitric oxide; FEV_1, forced expiratory flow in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

TABLE 4 Odds ratio of OSA for asthmatic children.

Characteristics	OR	95% CI	*p*-Value
Age (years)	1.025	0.799–1.315	0.845
Asthma controlled	0.130	0.050–0.337	0.097
Allergic rhinitis	8.217	3.216–20.996	0.000
Obesity	1.601	0.387–6.620	0.735
Gender	1.710	0.741–3.945	0.286
FEV_1 < 80%	0.383	0.165–0.888	0.06

FEV_1, forced expiratory flow in 1 s; OR, odds ratio.

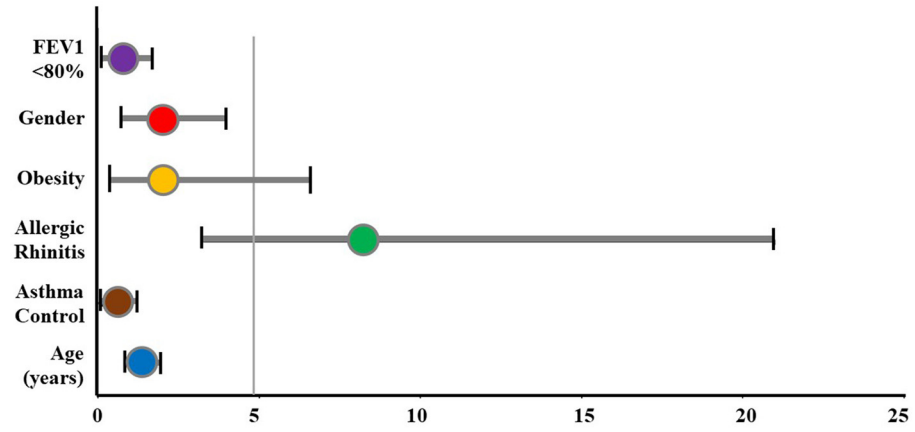

FIGURE 2
The odds ratio of OSA for study subjects. FEV1, forced expiratory volume in 1 s; OSA, obstructive sleep apnea.

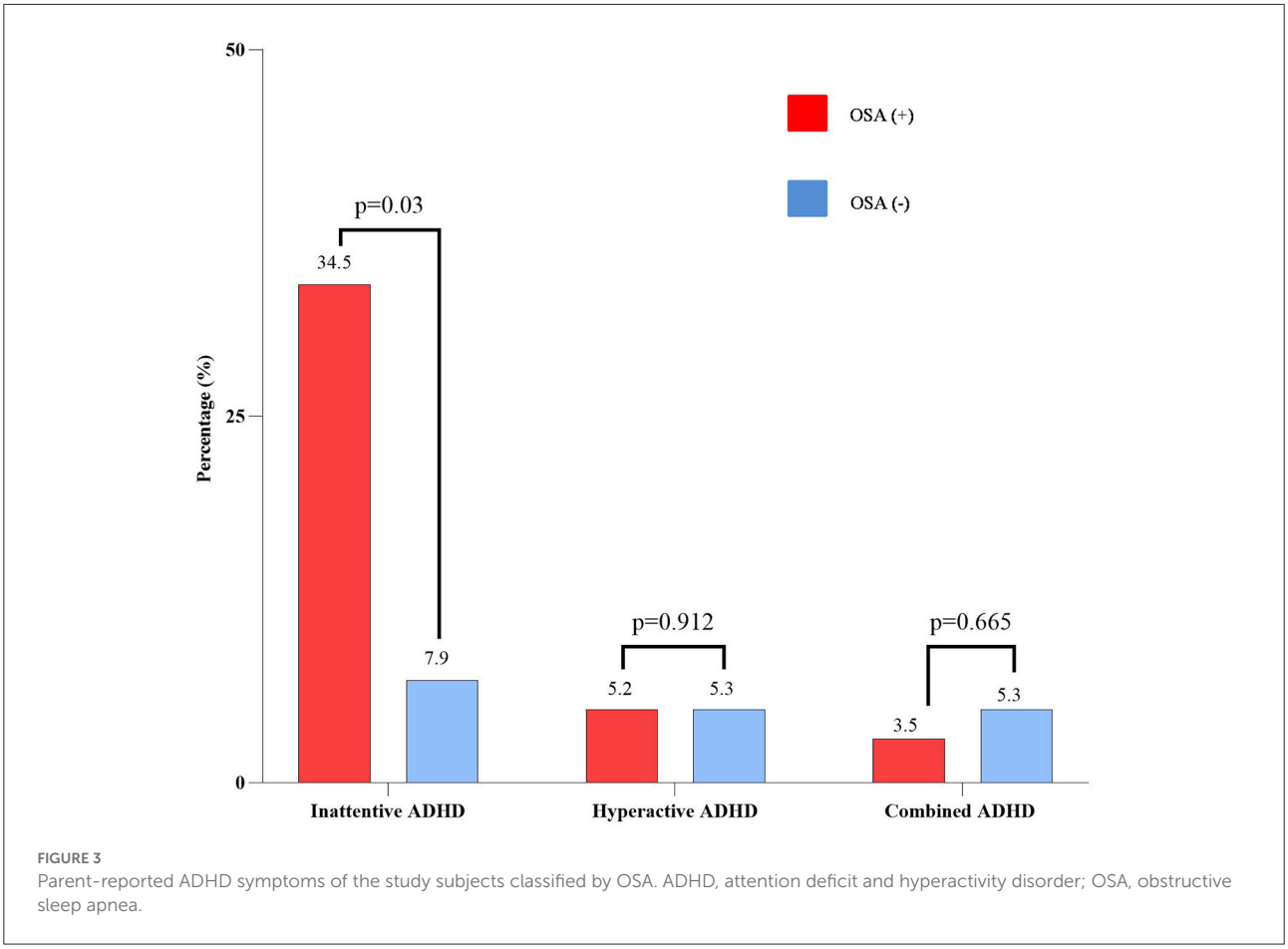

FIGURE 3
Parent-reported ADHD symptoms of the study subjects classified by OSA. ADHD, attention deficit and hyperactivity disorder; OSA, obstructive sleep apnea.

TABLE 5 Demographic characteristics, asthma control, and respiratory polygraphy of the study subjects classified by parent-reported ADHD symptoms.

Characteristics	OSA + ADHD	OSA alone	*p*-Value
n	25	33	
Age (years)	8.9 ± 1.2	7.9 ± 3.4	0.380
Male (female), ratio	17/8 (2.1)	21/12 (1.8)	0.665
Allergic rhinitis (*n*, %)	21 (84.0)	26 (78.8)	0.112
BMI score	17.6 ± 3.3	17.1± 3.5	0.225
Asthma (*n*, %)			
Well-controlled	10 (43.5)	13 (56.5)	
Partly or uncontrolled	15 (42.9)	20 (57.1)	0.174
ACT-score	18.9 ± 4.7	19.9 ± 5.3	0.549
Respiratory polygraphy			
AHI (mean)	4.1 ± 2.6	2.2 ± 1.8	0.042
Lowest oxygen saturation, %	68.6 ± 29.5	84.6 ± 34.1	0.0063

ADHD, attention deficit and hyperactivity disorder; AHI, apnea-hypopnea index; BMI, body mass index; OSA, obstructive sleep apnea.

inflammation of the upper airway tissue (28, 29). Systemic inflammation has been associated with OSA by studies that have identified upregulation of plasma CRP, increased neutrophils in the sputum, increased urinary levels of cysteinyl leukotriene, and

TABLE 6 Odds ratio of ADHD for study subjects.

Characteristics	OR	95% CI	*p*-Value
Asthma controlled	0.671	0.261–1.724	0.477
Allergic rhinitis	1.865	0.746–4.663	0.263
Obesity	0.197	0.024–1.630	0.157
OSA (AHI ≥1 event/hour)	3.355	1.271–8.859	0.015
AHI (event/hour)	0.606	0.503–0.731	0.000

ADHD, attention deficit and hyperactivity disorder; AHI, apnea-hypopnea index; OR, odds ratio; OSA, obstructive sleep apnea.

increased levels of leukotrienes and prostaglandins in exhaled breath condensate in children with OSA (29). At present, asthma had been proven to be an inflammatory disease (30). The higher prevalence of OSA in children with asthma indicates that this high-frequency co-infection requires special attention because it can make asthma more difficult to control (4, 17). In asthmatic patients, OSA plays a role as a contributing factor to aggravating asthma because airway obstruction in nocturnal asthma is linked to disturbances in sleep distribution, difficulty sleeping, insomnia, early waking up, and daytime sleepiness (9–11). However, there are still many arguments about the bidirectional interaction between asthma and OSA (9).

Obesity is considered an independent risk factor for both asthma and OSA; moreover, obesity makes a strong link between asthma and OSA (7–9). In the present study, only a few children with overweight or obese in the asthma group with OSA (Table 2). This result was different from other studies in Western countries, which showed that high BMI increased the prevalence of OSA (3, 4, 13), but similar to other Vietnamese studies (16, 31).

Numerous studies demonstrate that allergic rhinitis and asthma usually coexist (1, 2, 17). In the present study, 62.5% of the comorbidities were allergic rhinitis. The frequency of reported symptoms of allergic rhinitis in the asthmatic children with the OSA group was significantly higher than those without OSA (81.0 vs. 34.2%; $p < 0.05$). Previous studies in sleep-related problems had established the role of nasal obstruction due to allergic rhinitis in increasing the risk of upper airway obstruction during sleep, snoring, and OSA (32). The results of measuring the OR in the present study demonstrated that allergic rhinitis was the significant risk for the presence of OSA (OR: 8.217; 95% CI: 3.216–20.996; $p < 0.05$) (Figure 2).

The GINA guidelines emphasized the role of the lung function test to determine the level of asthma control (17); however, the relationship between asthmatic's patient lung function results and OSA is unclear (32). In a previous study (33), Sheen et al. enrolled 220 asthmatic children and revealed that FEV1/FVC is associated with the pediatric sleep questionnaire score (33). However, another research did not find any difference between the lung functions of an asthmatic patient with a high risk of OSA and those with a low risk of OSA (32). In the present study, we got the same result (Table 2). This also suggests that the degree of obstruction of the lower airway (bronchus) is not related to the severity of OSA in asthmatic children with OSA. Therefore, spirometry alone does not screen or suspect patients with OSA or the severity of OSA. The pathogenesis of OSA explains this due to the predominant obstruction of the upper respiratory tract (3).

High bronchial FENO in asthmatic children is a marker for allergic inflammation due to eosinophilia that has not been well-controlled by ICS or requires elevating ICS dose (23). However, a systematic search collected studies published from 1996 to 2016 from the PubMed, EMBASE, the Cochrane Library, and MEDLINE databases (34) revealed that FENO levels were significantly higher in patients with OSA compared to that in the control groups (6.32 ppb, 95% CI: 4.46–8.33, $p < 0.001$) (34). Consequently, elevating bronchial FENO would be a biological marker for suspecting OSA in a well-controlled asthmatic patient (34). OSA treatment with long-term CPAP therapy also reduced FENO levels (−5.82 ppb, 95% CI: −9.6 to −2.01, $p < 0.001$) (34). In the present study, the average bronchial expiratory nitrite concentration (FENO) of the asthmatic group with OSA was higher than the asthmatic group without OSA (21.6 ± 12.0 ppb vs. 14.2 ± 11.6 ppb, $p < 0.05$) (Table 2).

Uncontrolled OSA in children may cause adverse physical and mental consequences, especially ADHD or ADHD-like symptoms (13). The prevalence of ADHD is about 3% worldwide, while almost 95% of pediatric OSA patients had attention deficit disorders (13). The present study pointed out a significantly higher prevalence of the inattentive ADHD subtype in the asthmatic group with OSA (Figure 3). OSA was considered as a risk for the presence of ADHD (OR: 3.355; 95% CI: 1.271–8.859; $p < 0.05$), rather than asthma control (Figure 4). This result was similar to other studies (31, 35). Moreover, OSA + ADHD group had a markedly higher AHI score and significantly lower saturation oxygen than the OSA-alone group. Previous studies suggested that hypoxia in OSA is related to ADHD (13, 14). Sleep apnea may increase the rapid movement eye (REM) ratio and decrease the nocturnal SaO_2 (14), which may cause brain function impairment (14). This dysfunction leads to cognitive failure, executive disorders, and emotional disorders (13, 14), which play an important role in the pathophysiology of ADHD in children with OSA (3, 13, 14). Although hyperactive ADHD is more common in children aged below 6 years, in the present study, the prevalence of children with combined ADHD and hyperactive ADHD were 5.2 and 4.2%, respectively. This could be due to the parents just thinking that their children were naughty. Therefore, when children had poor academic performance, their parents might take them to the hospital for consultation regarding the diagnosis of ADHD. However, further studies with a large number of patients should be done to measure the exact prevalence of ADHD in children with asthma and OSA.

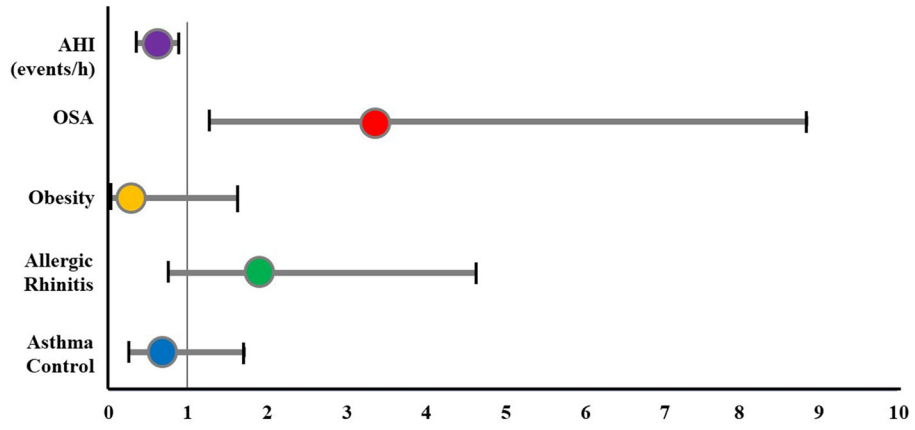

FIGURE 4
The odds ratio of ADHD for study subjects. ADHD, attention deficit and hyperactivity disorder; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.

This study, though, was subjected to some limitations. First, the present study was an observational, cross-sectional study with a small sample size. Moreover, overnight polysomnography or respiratory polygraphy is still expensive and time-consuming. Consequently, the diagnosis of pediatric OSA in Vietnam is still difficult and requires a lot of effort. Second, the present study missed gastroesophageal reflux, one of the most common risk factors for both asthma and OSA in children. Finally, because the present study was a cross-sectional study, the role of the patient's therapy in ADHD symptoms of study subjects was investigated. Thus, further studies should be conducted to clarify these limitations.

Conclusion

In summary, we reported the initial observations that the prevalence of OSA is significantly high in poorly controlled asthmatic children. Allergic rhinitis is also associated with a higher risk of OSA. The bidirectional relationship between asthma and OSA may make it exceedingly difficult to manage, especially in children with asthma–OSA overlap associated with ADHD. Thus, both diseases should be diagnosed and treated promptly.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Hanoi Medical University Institutional Ethical Review Board (IRB-VN01.001/IRB00003121/FWA00004148). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

LN-N-Q, MN-T-T, MN-T-P, CL-Q, HL-T-M, and SD-Q: conceptualization, validation, writing the original draft preparation, methodology, writing, reviewing, and editing. LN-N-Q, MN-T-T, and SD-Q: software. LN-N-Q, MN-T-T, MN-T-P, CL-Q, and SD-Q: formal analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sleep disturbance in post COVID-19 conditions: Prevalence and quality of life

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Post COVID-19 conditions are complaints and symptoms in patients with a history of probable or confirmed COVID-19 after 3 months of the onset of COVID-19 and last at least 2 months. About 10–20% of people may experience post COVID-19 conditions, one of which is sleep disturbance. There is a wide range of prevalence of sleep disturbances from 6% to more than 70%. An online survey of the post COVID-19 conditions in various countries showed that 78.58% of subjects had sleep disturbances, including insomnia, sleep-disordered breathing, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders. Sleep disturbance can be found starting from 2 weeks until 48 weeks or more after discharge or after having a negative COVID-19 test results. Women aged <50 years old with severe COVID-19 infection reported a worse outcome. Several mechanisms may cause sleep disturbance in post COVID-19 condition, namely persistent viral infection and inflammation, immunity dysregulation, and mitochondrial dysfunction. Several studies discovered sleep disturbance was a major problem that affected different domains of QoL in post COVID-19 conditions. Significant correlation was found between several dimensions of SF-36 with moderate-to-severe insomnia in post COVID-19 conditions. Therefore, sleep disturbance is a major problem in post COVID-19 conditions and may affect patients' QoL, and the existence of sleep disturbance should be a concern in post COVID-19 conditions period. Further research is required to determine the prevalence based on agreed definition as well as methods to assess this condition and its impact on QoL.

KEYWORDS

post COVID-19 condition, COVID-19, sleep disturbance, prevalence, quality of life

1. Introduction

Some patients who have suffered from Coronavirus Disease 2019 (COVID-19) may experience prolonged complaints and symptoms known as post COVID-19 conditions. Post COVID-19 conditions is a term of complaints and symptoms that have just appeared or continued after 3 months since the clinical onset of COVID-19 and have lasted for at least 2 months, or a history of close and confirmed contact (1, 2) World Health Organization (WHO) data shows the prevalence of post COVID-19 conditions estimated at 10–20%, with sleep disturbances among the six most complained of disorders in this condition (1). There is a wide range of prevalence of sleep disorders among different countries. Furthermore, there was a study conducted online with respondents from several countries found that 78.6% of patients with post COVID-19 conditions experienced sleep disturbance (2).

The biological process of sleep is crucial for preserving internal balance and overall well-being. In post COVID-19 conditions, several mechanisms, including persistent viral infection, persistent inflammation, involvement of the autoimmune system, and mitochondrial dysfunction can interfere with the part of the brain that regulates the sleep-wake cycle, causing sleep disturbance (3). On top of that, if sleep disturbance is not adequately managed, it can interfere with immune system and will further affect the sleep-wake cycle, which will continue creating a vicious circle and decrease overall QoL.

During the post COVID-19 condition period, sleep disturbance have a significant negative impact on variety of QoL aspects (4). A study conducted by Sigfrid et al. showed that patients with post COVID-19 conditions have a significant 10% decrease in QoL (5). According to Davis et al., 45.2% of the patients with post COVID-19 conditions needed to work fewer hours than they did before getting sick, and a further 22.3% were off work at the time of the survey because of the sickness (2). The Short Form-36 (SF-36)'s several dimensions of QoL had a statistically significant positive association with Insomnia Severity Index (ISI) scale. In addition, Global Pittsburgh Sleep Quality Index (Global PSQI) and mean duration of post COVID-19 conditions also showed a statistically significant positive correlation with various domains of the SF-36 QoL scale (4).

Understanding QoL is crucial for enhancing patient care, symptom alleviation, and rehabilitation. Patients' self-reported QoL issues may prompt therapy and care revisions and improvements, or may demonstrate that some therapies are ineffective. Identifying the variety of issues that may affect patients also involves using QoL (6). Therefore, in this review, we discuss the currently available published literature related to sleep disturbance in post COVID-19 conditions, the prevalence, the possible mechanism, and its association with QoL.

2. The post COVID-19 conditions definition

Since the global outbreak of novel coronavirus pneumonia in 2019, known as Coronavirus Disease (COVID-19), the knowledge about the long-term effects of the disease has rapidly grown. There are several definitions and terms for long-term symptomatic COVID-19. This condition was described for the first time by Greenhalgh et al. as post-acute COVID-19 and chronic COVID-19, with post-acute COVID-19 lasting more than 3 weeks after the start of the first symptoms and chronic COVID-19 lasting more than 12 weeks (7). According to the Scottish Intercollegiate Guidelines Network, the Royal College of General Practitioners, and the National Institute for Health and Care Excellence (NICE), long COVID is defined as signs and symptoms that developed during or after a disease that is consistent with COVID-19 and that persist for more than 4 weeks but cannot be accounted for by other diagnoses (8). Therefore, WHO stated that post COVID-19 conditions are complaints and symptoms that occur in patients with a history of probable or confirmed COVID-19 after 3 months of the onset of infection and last at least 2 months (1). These complaints and symptoms of the post COVID-19 conditions cannot be explained by other alternative diagnoses, and have an impact on the patient's daily functioning. Symptoms may persist after infection or appear after a period of recovery. Symptoms can also fluctuate (change in quality and quantity over time) or recur (recurrence of disease manifestations after symptom improvement) (1, 2).

Multiple organs may be affected by the post COVID-19 conditions (2). According to WHO, the most common symptoms and complaints were fatigue (78%), shortness of breath (78%), and cognitive dysfunction (74%). In addition, other symptoms that are often complained of are memory disturbances (65%), muscle pain or spasms (64%), and sleep disturbances (62%) (1, 2). A significant increase of psychological manifestation such as anxiety and depression was noticeably reported in post COVID-19 conditions (9, 10). Noticeably, a meta-analysis study found fatigue, cognitive dysfunction, and sleep disturbance appeared to be the key features of post COVID-19 conditions (1, 9).

3. Discussion

3.1. Prevalence and types of sleep disturbance in post COVID-19 conditions

Globally, more than 160 million cases of COVID-19 have been confirmed and there have been more than 3 million deaths. The majority of COVID-19 patients have mild to moderate symptoms, whereas 14% of patients have severe symptoms and 5% are in serious condition (11). The median time to

recover from COVID-19 is 13 days, with an interquartile range of 9–17 days (12). Despite already having negative PCR test result, 1 in 5 people may have symptoms for 5 weeks or more, while 1 in 10 may be symptomatic for 12 weeks or more (13). In a study conducted by Whitaker et al., 37.7% of 76,155 people with post COVID-19 conditions experienced at least one persistent symptom, while 17.47% experienced three or more symptoms, lasting up to 12 weeks (14). This study also examined the prevalence of post COVID-19 conditions after a period of 12 weeks, they found 5.80% patients with one or more symptoms and 2.23% of patients with three or more symptoms (14). The prevalence of persistent symptoms was higher in women than in men and the risk of post COVID-19 conditions symptoms increased linearly with age (14, 15).

Sleep disturbance were among post COVID-19 conditions that were frequently recorded throughout the pandemic, both during the acute phase of COVID-19 and after recovery, which resulted in ongoing problems for the survivors' lives (16). Rousseau et al. conducted a follow-up study of subjects with severe COVID-19 who were hospitalized for more than 7 days and found that 75% had poor sleep quality. They suggested that the majority of severe COVID-19 survivors have sleep fragmentation and frequent arousals from sleep (17). Davis et al. conducted an online survey of the post COVID-19 conditions phenomenon in various countries. The study results showed that 78.58% of subjects had sleep disturbances (2). Another study conducted by Sigfrid et al. in the UK found that 46.2% of patients experienced sleep disturbances 3 months after initial COVID-19 symptom onset (5).

Studies in North-Africa and the Middle-East have found similar results. 35% of post COVID-19 conditions patients were still displaying sleep disturbance 2 months after discharge from a Bangladesh hospital, primarily in patients with diabetes mellitus (16). A cross-sectional observational study in the Saudi Arabia investigated the sleep disturbances in 32% patient and showed high scores of ISI and PSQI (4). According to a study conducted in Egypt with 85 recovered COVID-19 patients and 85 individuals without COVID-19, most recovered COVID-19 patients (77%) showed sleep disturbance, compared to 46% of controls (18).

Despite the fact that patients with post COVID-19 conditions frequently complain about sleep, but comprehensive data are still lacking. Data from several studies showed that the prevalence of sleep disturbance in post COVID-19 conditions has a wide range between 6% to more than 70% (Table 1). This wide range can be due to differences in methodology used in previous prevalence studies. Some studies included all patients with post COVID-19 conditions, while others only included patients who had sleep disturbances during the acute infection period and were observed throughout their recovery time. Most of the studies in Table 1 mention the types of sleep disturbance experienced by patients in the form of insomnia, while only two studies focused on Obstructive Sleep Apnea (OSA). There was only one study described several types of sleep disturbance and their prevalence, with insomnia at 60%, waking up several times at night at 41%, awakening due to breathing difficulty at 36%, having restless legs syndrome (RLS) at 18%, sleep apnea at 10%, having vivid dreams at 33%, nightmares 26%, and lucid dreams 15% (2). Another cause for this wide range of prevalence might be due to the variations in evaluation time following the onset of COVID-19 in the studies shown in Table 1, starting from 2 weeks until 48 weeks or more after discharge or after having a negative COVID-19 test results (19, 27).

3.2. The possible mechanism of sleep disturbance in post COVID-19 conditions

Although no specific pathophysiological theory can define post COVID-19 conditions, attention has been directed toward several mechanisms, including persistent viral infection, persistent inflammation, involvement of the autoimmune system, and mitochondrial dysfunction (3). One of the mechanisms, namely persistent viral infection indicated by persisting SARS-CoV-2 RNA for up to 230 days after the onset of symptoms in several anatomic areas, including the brain's various regions (38). Since the virus also affects the hypothalamus and brainstem, it may disrupt the sleep-wake cycle, resulting in insomnia or poor quality of sleep (39).

Persistent proinflammatory cells [IL-1, IL-6, and Tumor Necrosis Factor-α (TNF-α)] and altered cytokine production is suspected to have occurred during persistent inflammation in post COVID-19 conditions, revealed by a cytokine profiling study (40, 41). Inflammation can modify sleep by increasing Non-Rapid Eye Movement (NREM) sleep and decreasing rapid eye movement (REM) sleep, and vice versa sleep disturbance can also modify the inflammation process by altering circulating cytokines (41, 42).

There are evidence pointing that post COVID-19 conditions involves autoimmunity (43). Dysregulation of this autoimmune response may cause sleep dysfunction. Both humoral and cellular immune-mediated response can target sleep-regulating neural structures (e.g., brainstem, hypothalamus) as well as neurotransmitter systems (e.g., hypocretin) (40, 44).

Mitochondrial dysfunction in post COVID-19 conditions was reported in a small cohort that discovered lower fatty acid oxidation and elevated lactate levels early in workout, showing that mitochondrial dysfunction was present and metabolic reprogramming had occurred (45). Damaged mitochondria can release a wide range of damage-associated molecular patterns

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TABLE 1 Type and prevalence of sleep disturbance.

No	Reference	Type of sleep disturbance	Evaluation time after onset of COVID-19	Prevalence
1.	Xu et al. (19)	Insomnia	2 weeks	26.45% of 121
2.	Zhang et al. (20)	Poor sleep (unspecified)	3 weeks	55.6% of 135
3.	Huynh et al. (21)	Insomnia	2–4 weeks	34.5% of 325
4.	Lorenzo et al. (22)	Insomnia	3–4 weeks	27.6% of 195
5.	Mazza et al. (23)	Insomnia	4 weeks	40% of 402
6.	Ng et al. (24)	Sleep disturbance (unspecified)	4 weeks	77.7% of 18
7.	Halpin et al. (25)	Obstructive sleep apnea	4–8 weeks	15.3% of 100
8.	Kalamara et al. (26)	Insomnia	4 weeks 12 weeks 24 weeks	56.5% 53.5% 39.2%
9.	Buensenso et al. (27)	Insomnia	4–20 weeks 24–36 weeks ≥48 weeks	9.3% of 355 5.7% of 157 5.2% of 154
10.	Islam et al. (16)	Sleep disturbance (unspecified)	8 weeks	35% of 322
11.	Arnold et al. (28)	Insomnia	8–12 weeks	24% of 110
12.	Pellitteri et al. (29)	Insomnia	8 weeks 40 weeks	19.1% of 47 27.3% of 44
13.	Magdy et al. (30)	Insomnia	12 weeks	Migraine patient: 23.5% of 204 Non-migraine patient: 12.3% of 204
14.	Moy et al. (31)	Insomnia	>12 weeks >24 weeks 48 weeks	8 of 126 19% of 60 45% of 60
15.	Alkodaymi et al. (32)	Sleep disorder (unspecified)	12–24 weeks 24–36 weeks 36–48 weeks >48 weeks	24% of 257,248 29% of 257,248 0% 30% of 257,248
16.	Sayed et al. (4)	Insomnia	16 weeks	32% of 500
17.	Mattioli et al. (33)	Insomnia	16 weeks	6.6% of 120
18.	Labarca et al. (34)	Obstructive sleep apnea	16 weeks	61.6% of 60
19.	Taquet et al. (35)	Insomnia	24 weeks	5.42% of 236,379
21.	Huang et al. (36)	Sleep disturbance (unspecified)	24 weeks	26% of 1,655
22.	Elkan et al. (37)	Sleep disturbance (unspecified)	36 weeks	8% of 66
23.	Davis et al. (2)	Insomnia Night sweats Awakened feeling unable to breathe Restless legs Sleep apnea Vivid dreams Nightmares Lucid dreams	N/A	60% 41% 36% 18% 10% 33% 26% 15%

that are potent activators of the inflammatory response (46). This process can damage the neurons in the sleep-regulating area of the brain, which affects the circadian rhythm, sleep apnea, and obstructive sleep apnea (47, 48). Figure 1 summarized all possible pathogenic mechanisms of sleep disturbance in post COVID-19 conditions.

3.3. Factors contributing to sleep disturbance in post COVID-19 conditions

Several factors may contribute to sleep disturbances in post COVID-19 conditions. Disease severity, circadian rhythm disturbance, psychiatric disturbance, uncontrolled chronic diseases during acute stage, social isolation, social economic status, age and even gender may play a role. When individuals with moderately severe symptoms are treated in hospitals, hospitalization might alter the circadian rhythm, which may lead patients to have sleep disturbances. Circadian rhythms, which are primarily triggered by daylight, meals, and exercise (49) are frequently compromised or altered while a patient is hospitalized (50). COVID-19 patients tend to experience fear and anxiety about social isolation procedures, as well as mandatory lockdowns in the acute phase, leading to an increased incidence of sleep disturbances in the population (51–53). A study reported a higher prevalence of difficulty falling asleep, staying asleep, and getting up early in patients with moderately severe COVID-19 infection, whereas difficulty staying asleep and waking up earlier was experienced in patients with more severe disease (54). Another study showing that diabetes mellitus was independently associated with sleep disturbances among patients with post COVID-19 conditions showed that the presence of chronic illnesses can also have an impact on the persistence of sleep disturbance (16). COVID-19 patients conveyed that the disturbing factors that affect them are a sense of tightness, worries about illness, anxiety, the voices of other patients, medical staff, and medical devices (50). Another study using actigraphy found that patients with severe COVID-19 symptoms, including those with severe respiratory symptoms and those requiring Intensive Care Unit (ICU) displayed lower sleep efficiency, higher immobility time, and higher fragmentation index compared to those with mild symptoms and who do not require ICU care (55). Actigraphy may not be the gold standard for evaluating sleep, but it is simple to implement and could be sufficient for identifying changes in sleep schedules that would indicate disturbances of the circadian clock (56).

There is a bidirectional relationship between sleep disturbance and psychiatric disorders (57). A study described that patients with post COVID-19 condition who listed mental health issues such as stress, anxiety, or depression were more likely to develop sleep disturbance compared to those who did not (21). Another study reported that moderate to severe sleep disturbances associated with mood symptoms evaluated using the Patient Health Questionnaire (PHQ)-2 and the Anxiety Disorder (GAD)-2 questionnaires (58). It is critical that healthcare professionals evaluate and treat sleep disturbance among patients with post COVID-19 conditions in order to improve both their regular sleep patterns and mental health because adequate sleep is essential for facilitating patient recovery (21).

A study evaluated insomnia in post COVID-19 conditions reported that age and health status may be the influencing factors. Insomnia is more common in older individuals because they tend to experience a low self-evaluation and are more prone to be under multiple strains, including social economy and health-related problem (19). Among patients with post COVID-19 conditions, another study reported that women also predicted poor result of global PSQI (18). According to a study, women are more likely than men to survive severe acute illness, which may lead to worse long-term results. However, more investigation is required to demonstrate why women predominately experience the post COVID-19 conditions (5).

3.4. Quality of life of sleep disturbance in post COVID-19 conditions

The Quality of Life (QoL) was defined as "a patient's general subjective perception of the burden of sickness or medical condition on various areas, including physical, psychological, social, and occupational functioning" (6). The QoL of patients with post COVID-19 conditions has been significantly affected regardless of the period of time after discharge or recovery. A study conducted by Sigfrid et al. reported that patients with post COVID-19 conditions showed a significant 10% decrease in QoL (5). This measurement is based on 5 dimensions, consisting of mobility, self-care, activities of daily living, pain or discomfort, and anxiety/depression (5, 59). The most frequently discussed risk factors for poor QoL included female sex, advanced age, co-morbidities, Intensive Care Unit (ICU) admission, prolonged ICU stay, and mechanical ventilation (60).

There was still a significant persisting impact on QoL across all dimensions in patients with post COVID-19 conditions 12 weeks after onset in both survivors and family members (61). During the period of post COVID-19 conditions, sleep issues must be handled because they have severe effects on numerous areas of QoL. The SF-36's several dimensions of QoL had a statistically significant positive association with moderate-to-severe insomnia based on ISI scale. One third of total patient had moderate-to-severe insomnia showed significant positive association with several dimensions of SF-36, such as

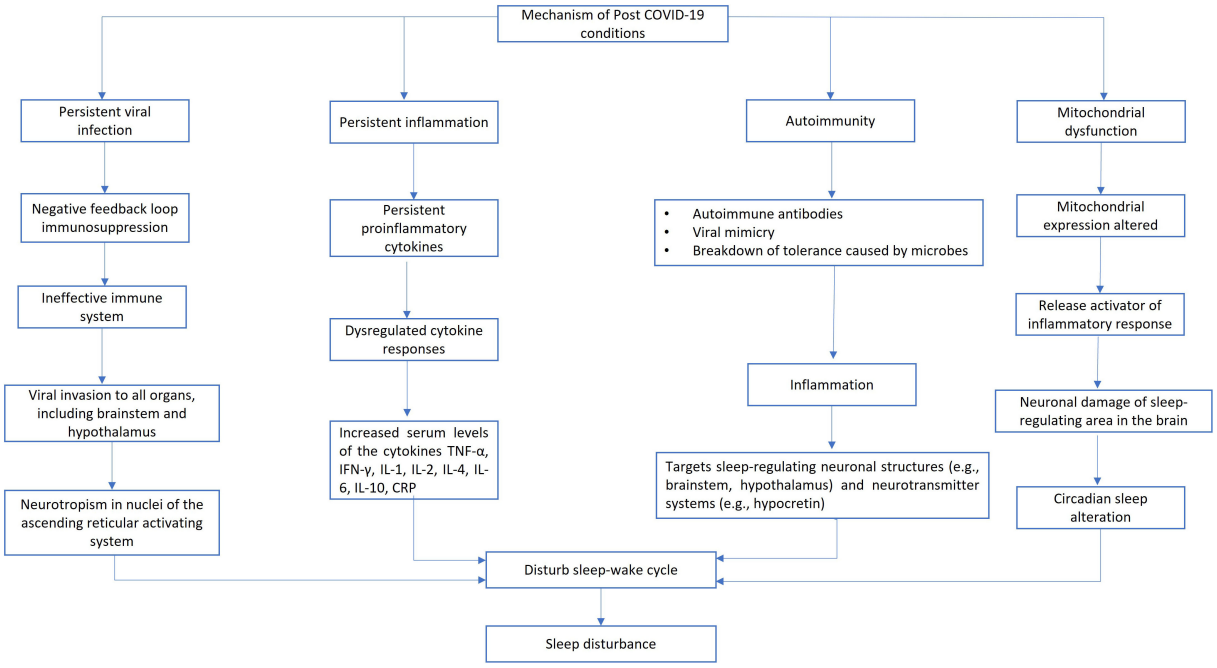

FIGURE 1
Possible pathogenic mechanisms of sleep disturbance in post COVID-19 conditions.

physical functioning, role limitation due to physical health, role limitation due to emotional problems, and general health. Global PSQI score of post COVID-19 conditions also showed a statistically significant positive correlation with various domains of the SF-36 QoL scale (4). Another study also indicated that poor sleepers based on PSQI examination significantly underperformed in several SF-36 areas relating to subjective physical and mental health indicators when compared to good ones (29).

There was a high proportion of patients with post COVID-19 conditions who also suffered from mental health issues such as stress, anxiety, and depression (21). A study using Short Form-8 (SF-8) to measure QoL found that post-Traumatic Stress Disorder (PTSD) has mediating effect on insomnia and QoL (62). Since sleep disturbances and mental health are strongly associated, intervention and prevention strategies concerning mental health issues may improve Health-Related Quality of Life (HRQoL) and sleep in patients with post COVID-19 conditions (62).

Regardless of the amount of time after discharge or recuperation, the QoL of the patients with post COVID-19 conditions was significantly impacted (60). Understanding QoL is crucial for enhancing patient care, symptom alleviation, and rehabilitation. Patients' self-reported QoL issues may prompt therapy and care revisions and improvements, or they may demonstrate that some therapies are ineffective (6). Therefore, it is important to take further preventive steps in order to stop the sleep disturbance in patients with post COVID-19 conditions from worsening and affecting QoL.

4. Conclusion

Sleep disturbances have a strong impact in decreasing post COVID-19 conditions' overall QoL. Various kinds of sleep disturbance can be found in patients with post COVID-19 conditions with a wide range of prevalence, between 6% to more than 70%. This wide range may be caused by differences in methodology and timing of assessments following the onset of COVID-19. No specific pathophysiological theory can define the post COVID-19 conditions or sleep disturbance in post COVID-19 conditions. Still, several mechanisms that play a role in post COVID-19 conditions can cause sleep disturbance, namely persistent viral infection, persistent inflammation, autoimmunity or immunity dysregulation, and mitochondrial dysfunction. In addition, other factors such as disease severity, circadian rhythm disturbance, psychiatric disturbance, uncontrolled chronic diseases during acute stage, social isolation, social economic status, age, and even gender may also play a role. Sleep disturbance positively correlates with several dimensions SF-36, a measurement tool for QoL. By better understanding the impact of sleep disturbance on QoL, the existence of sleep disturbance should be a concern in post COVID-19 conditions period. Besides,

it is important to take further preventive steps in order to stop the sleep disturbance in post COVID-19 conditions from worsening and affecting QoL. Further research is required to determine the natural history of this condition as well as to define risk factors, pathogenesis, the prevalence in various countries, and therefore determine possible interventional strategies.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sleep apnea in people with Down syndrome: Causes and effects of physical activity?

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Poor sleep quality is recognized as a major risk factor for poor health, increasing the incidence of serious chronic diseases. In people with Down syndrome, sleep apnea prevalence is significantly greater, it is caused by genetic, anatomical, endocrine, and metabolic abnormalities. The consequences of sleep disruption due to sleep apnea are very serious, especially in terms of neurocognitive and cardiovascular effects, leading to reduced life expectancy and quality of life in this population. However, the management, care, and treatment of related disorders in people with Down syndrome are still inadequate and limited. Therefore, this article wants to increase understanding and awareness about sleep apnea and the benefits of physical activity in improving sleep quality in the Down syndrome community, families, and their care specialists.

KEYWORDS

sleep disorders, sleep apnea, physical activity, Down syndrome, trisomy 21

1. Introduction

Sleep is a biological process essential to life. It plays a fundamental role in the functioning of the brain, metabolism, systemic functions, regulation of appetite, but also in the regulation of the immune, hormonal and cardiovascular systems (1). Besides it, sleep is essential for recovery and good mental health. Healthy, normal, good-quality sleep is characterized by duration, regularity, absence of sleep disturbances and/or decreased wakefulness hence decreased daytime sleepiness (2, 3). Sleep is also an essential element for learning, memory, emotional control, and mood maintenance. However, today, a large part of the population "sleeps badly" and goes to bed later and later, thus reducing the amount of sleep. The abuse of screens, work pressure or certain professional specificities requiring night work (sleep deprivation) affect sleep and ultimately health and quality of life (4). The decline in sleep quality in children, adolescents and adults is a real problem in our society because sleeping poorly is reported to affect approximately one-third of the general population (5). Its consequences lead to impaired cognition, lower quality daily activities, poorer work performance, and impaired physical and mental health (6, 7).

From clinicians who consider the increasingly frequent complaints related to an alteration of sleep quality to the large industrial companies who market more and more devices allowing the detection of sleep abnormalities and the quantification of their duration in outpatients, it can be seen that many individuals and organizations were indeed interested in this issue.

Actually, sleep is an essential time for the recovery and homeostasis of physiological processes. It is not a lost time but a time during which cerebral activities allow the processing of acquisitions, the consolidation of learning and their memorization. Controlled by two major factors, homeostatic factors, and circadian factors (biological clock), sleep is also strongly

influenced by many other factors (noise, state of health, stress, light, temperature...). Therefore, any quantitative and/or qualitative alteration of sleep has an impact on the daily performance, and increases many risks, in particular those related to health: obesity, diabetes, cardiovascular diseases, decrease in immunity, increase in mortality and ultimately poor quality of life.

Today, variations in many environmental and social conditions, have caused sleep disorders to become common and frequent (8, 9), but their management and treatment have long been underestimated. Compared to other health issues, sleep health is a topic that has only recently been studied (10), especially for vulnerable individuals such as those with disabilities.

People with disabilities have physical, motor, or intellectual specificities that can cause certain sleep disorders (such as breathing disorders) and affect their quality of life (11). According to the World Health Organization, up to 15% of the world's population has a specific form of disability with associated sleep disorders (12). For example, several studies have shown that 86% of children and adults with disabilities had symptoms related to sleep disorders (sleep apnea syndrome, narcolepsy...) resulting in sleep deprivation, and daytime sleepiness... (13). The health consequences for populations with disabilities are multiple (14–16). Sleep disorders, if left untreated, can progress to serious chronic diseases that increase the risk of death and decrease life expectancy in people with disabilities (17).

Down syndromes (DS) represent a significant population in the disability community. They are characterized by a high prevalence of sleep problems, such as sleep apnea syndrome, which manifest from early childhood through late life. Sleep apnea syndrome (SAS) in people with DS is characterized by frequent pauses in breathing during sleep, causing oxygen desaturation and arousals (18). Hypoxemia due to these apnea episodes can occur several hundred times during the night, increasing the risk of cardiovascular complications and hypertension in these subjects (19). In addition, dysfunctions of physiological functions and anatomical abnormalities in people with DS facilitate overexpression of SAS and exacerbate acquired pathologies in this population (20). Studies on the treatment and management of sleep disorders in people with disabilities, particularly with Down syndrome, show several options. One of the most frequently used treatments for sleep disorders is the prescription of drug treatments, which are certainly effective, but which have many potential side effects. In people with Down syndrome, the therapeutic option is more complex because of the cognitive handicap, the anatomical malformations, and the frequent non-observance of the proposed treatments. Therefore, understanding the etiology and characteristics of specific sleep disorders in this population is extremely important to find more effective treatments.

2. Characteristics of sleep disorders in people with Down syndrome

2.1. Historical background and definition

Trisomy 21 (T21), or Down syndrome, was initially described in 1838 by the French physician Jean-Etienne Esquirol, and in 1846, Dr. Edouard Seguin, proposed a clinical description of Trisomy 21 based in part on the writings of Jean-Etienne Esquirol (21). In 1866, the English physician John Langdon Down published the article "Observations on an ethnic classification of idiots" in the London Hospital Reports (22) and gave the name "Mongolian type" to the profile of T21 children. He observed that this handicap always appeared congenitally, and never after birth.

On January 26, 1959, the French doctors Jérôme Lejeune, Marthe Gautier and Raymond Turpin published an article in the Bulletins de l'Académie des Sciences (23) which was to become a milestone in the treatment of children with trisomy 21. They presented the cases of three children with Down syndrome and demonstrated that this syndrome is caused by the presence of a supernumerary chromosome 21. Down syndrome was then renamed "trisomy 21."

Trisomy 21 is the first chromosomal anomaly described in humans. It is also the first syndrome for which a link between genotype and phenotype has been established.

Trisomy 21 is defined not as a disease but as a syndrome. It is a genetic syndrome, due to the presence of a supernumerary chromosome 21. A person with Down syndrome can live in good health, in a complete state of physical, mental and social wellbeing. It only requires adaptations to his condition concerning his physical environment, his social environment, his organization, language etc.

2.2. Epidemiology and etiology

Trisomy 21 is the most common chromosomal anomaly, and it manifests itself from the beginning of pregnancy (Figure 1). Its prevalence is 1 in 700 births, which represents about 1,100 new cases per year in France, for a total population of about 60,000 people with T21. In France, the number of births of children with T21 is decreasing thanks to efficient screening and prenatal diagnosis. However, the risk of giving birth to a child with T21 increases with the mother's age. Thus, at 20 years of age, the risk of having a pregnancy with a trisomy is 1/2,000, whereas this risk increases to 1/20 at 45 years of age.

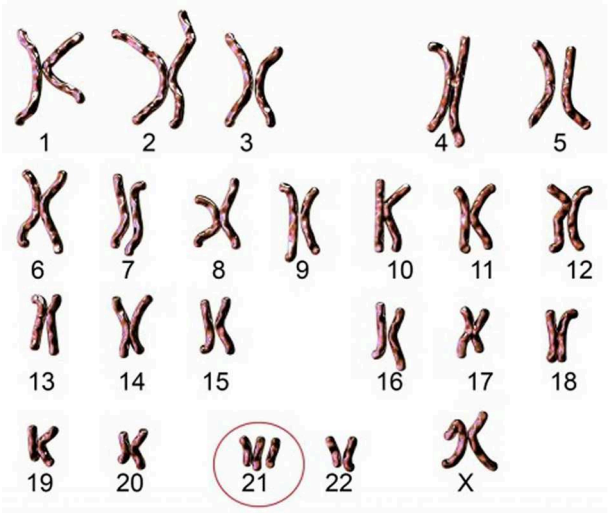

FIGURE 1
Karyotype of an individual with free and homogeneous trisomy. Source: Imago/Science Photo Library.

Today, it is reported in France one birth of T21 child per day, despite this very well-organized antenatal screening. This screening includes numerous examinations during the pregnancy (questioning, ultrasound, and biological examinations), and especially in case of doubt, a screening with specific serum markers. Thanks to these examinations, a risk calculation is obtained, and it is then possible to perform a fetal karyotype to establish the type of T21. This karyotype makes it possible to identify the precise type of T21 among the three known forms which are free and homogeneous trisomy, mosaic trisomy and trisomy by translocation. Each of these three forms is distinguished by different clinical features. All of them are the result of an abnormality brought on by chromosome 21.

This chromosome 21 alone expresses 1.5% of the human genome, the information is thus carried on 47 million nucleotides representing 300–400 genes that code for different proteins. The genetic importance of chromosome 21 explains why this gain of genetic material leads to a significant biochemical imbalance with multiple and irreversible consequences.

2.3. Risk factors and sleep apnea

Children with Down syndrome present clinical signs whose expression and severity vary according to the type of Down syndrome. However, according to the proposed treatments, thanks to early diagnosis, thanks to physical activity and/or cultural activities programs... the life expectancy of these children has increased considerably over the last decades.

However, this improvement is based on a heavy and constraining medical course for the child and his parents, because trisomy 21 predisposes to hormonal, cardiac and metabolic dysfunctions, numerous and sometimes severe. It is associated with a wide spectrum of cognitive deficiencies (learning, memory, and language), delays in motor and neurological development (24, 25). Structural abnormalities of the brain (reduced brain volume, especially at the frontal, temporal and cerebellum levels) are predictive of dementia, and signs of Alzheimer's disease are much more frequently described in the population with T21. These abnormalities are known to be the cause of poor cognitive activity and rapid decline (24, 26).

The severity and frequency of clinical signs vary, but almost all are related to the development of sleep disorders that are more common in this population. In 2020, Dumortier and Bricout (19) published a review of the literature regarding the presentation of these links between T21 and sleep apnea syndrome. The authors of this review highlighted the causes and consequences between T21 and OSAS, specifying their birelation (OSAS in adult with Down syndrome: causes and consequences: Is it a "chicken and egg" question?).

Other studies showed the physical phenotype of T21 is very characteristic:

- The face is round, flat, and with little relief,
- The skull is small and the occiput flat,
- The eyes are oblique, spaced, and the eyelid is without fold,
- The ears are round and small,
- The nose is small,
- The tongue is very particular: thick, and rough, with many folds (macroglossia),
- The mouth presents anatomical anomalies, small size, dental problems, and prognathism.

In addition, there are anatomical vertebral particularities (instability of the first two cervical vertebrae, prevalence of narrow lumbar canal) that induce pain during activities (walking, shift work or physical activities). Both children and adults are small in stature and are characterized by overweight or obesity.

Associated with these specific physical characteristics, other clinical signs have been reported (endocrine, metabolic, autonomic). In this manuscript, we will limit ourselves to those that have a direct impact on sleep disorders.

2.3.1. Endocrine disorders

Endocrine disruption has been reported in individuals with DS and it is strongly linked to obesity due to dysautonomia and the increase in fat mass, thereby indirectly causing SAS. Abnormal levels of hormones involved in metabolism, storage and lipolysis, such as leptin and insulin, have been observed to increase the risk of sleep apnea and cardiovascular complications (27). The best-described endocrine pathologies in Down syndrome are thyroid dysfunctions (hypothyroidism, hyperthyroidism) (28, 29). Hypothyroidism has major effects on basal metabolic rate and is thought to promote overweight. Hyperthyroidism induces tachycardia with palpitations and is very frequently diagnosed in conjunction with sleep disorders. These thyroid dysfunctions have multiple consequences: slowed cognitive development, fatigability, lowered energy metabolism, slowed development and growth.

Abnormalities in catecholamine secretion are also reported, with a decreased amplitude of adrenergic responses that blunt cardiovascular responses during stress or exercise (30, 31).

Furthermore, in men with T21, a decrease in testosterone secretion associated with hypogonadism is described. This acts directly on body composition, favoring the accumulation of fat mass (32). This development of fat mass has many consequences on the appearance of obstructive apneas by an accumulation effect in the upper airways.

2.3.2. Metabolic dysfunctions

A sedentary lifestyle is the source of the metabolic syndromes associated with obesity, low-grade inflammation, and diabetes in people with DS. It maintains a loop of "ataxia—overweight—sedentary" and results in lower muscle mass, increased fat mass and finally SAS (33). Studies have shown that hypoxia caused by SAS induces inflammatory cytokine release leading to dysglycemia and insulin resistance in the T21 population. Meanwhile, insulin resistance also increases the risk of diabetes and obesity, which contributes to SAS (34).

In addition, generalized hypotonia increases the risk of airway collapse and airway obstruction (complete or partial) can occur during sleep, due to decreased muscle tone in the oropharynx, leading to snoring and OSA in individuals with DS (35). It also alters the quality of motor skills and effort in people with T21 (36–39). These impairments make activities of daily living more taxing and difficult to continue, with fatigability occurring more rapidly during exertion. Spontaneously, people with T21 are less inclined to engage in physical activities, and they then fall into a loop of deconditioning, sedentary

lifestyle, weight, fatigue and activity limitation. Numerous studies have confirmed this vicious circle of deconditioning, which results in a lower tolerance to effort in people with T21 (36, 40).

In T21, there are more frequent digestive dysfunctions and also contribute to the development of metabolic syndrome, in particular the presence of gastroesophageal reflux (41). There is more evidence for a link between SAS and gastroesophageal reflux disease. In which, the large negative intrapleural pressure fluctuations during apnea will cause reflux phenomena (42). This may also be involved in the reduced desire to practice physical activity, as the subjects describe more reflux during exercise. These digestive disorders are also particularly observed when there is low-grade inflammation, with high inflammatory markers (43), or dysautonomia, with an altered vagal tone favoring gastroesophageal reflux.

2.3.3. Autonomic nervous system dysfunctions or dysautonomias

Nervous system dysfunction has been the subject of numerous studies in the T21 population, it often presents with dysautonomia at rest, during sleep, during exercise, or during stimulation tests with an inappropriate vagal response, which effectively reflects maladaptations of the autonomic nervous system dysfunctions (ANS) (44–47). Cardiovascular and neurological parameters are cyclically altered, corresponding to respiratory events due to sleep apnea syndrome at T21, particularly with low blood pressure and heart rate than in the general population. During exercise, there is joint chronotropic incompetence and poor hormonal regulation (catecholamines, cortisol, and glycemic regulation hormones) that increase the consequences of autonomic maladaptation leading to early fatigue and limitation to exercise (30, 40, 48). Hypoxia during apnea causes bradycardia, followed by tachycardia on the resumption of breathing (49). The increase in heart rate at the end of apnea may be due to catecholaminergic release and sympathetic stimulation following a respiratory event. Sleep apnea increases arterial pressures and activates nocturnal sympathetic tones that increase pulmonary arterial pressure (50). This increases the risk factors for coronary heart failure, cardiovascular death, and stroke.

One of the proposals has been to implement regular physical activity (PA) whose beneficial effects could also have various impacts: increased practice times, loss of body fat, a gain of muscle mass, a gain of strength, improvement of sleep... (51).

All of this clinical picture drawn up to characterize trisomy 21, explains to a large extent the appearance of sleep apnea syndrome in this population.

3. Sleep apnea syndrome and Down syndrome

In T21, sleep apnea syndrome shows an exceptionally high prevalence ranging from 40% to 88% in adults (52) and up to 97% in children (53) while only 7–13% of the general population is affected by this syndrome (54). However, sleep apnea is still misdiagnosed in T21 while it is responsible for cardiovascular pathologies and reduced life expectancy (55). The consequences of SAS can be observed in various abnormalities such as sleep fragmentation, nocturnal awakenings, snoring, morning asthenia, daytime hyper sleepiness and mood disorders.

Obstructive sleep apnea syndrome is characterized by partial or complete obstruction of the upper airway that is intermittent and repeated during sleep (18). These events are typically associated with a decrease in blood oxygen saturation and can occur several hundred times in a single night of sleep. Apnea episodes can occur during NREM or REM sleep, but are generally more deleterious to health when they occur during REM sleep (56). There are three possible types of apneas that can be observed during sleep: obstructive, central, or mixed apneas, and these hypopneas characterized by the apnea-hypopnea index (AHI), it is the total number of abnormal events measured during 1 h of sleep. To make a precise diagnosis of these sleep disorders, polysomnography (PSG) is used to calculate AHI and classified according to the following levels: AHI $>$ 5 = mild SAS, AHI $>$ 10 = moderate SAS, AHI $>$ 15 = severe SAS, AHI $>$ 30 = very severe SAS (57, 58).

While PSG is indeed the gold standard for diagnosing SAS, there are still other warning signs that exist. Nocturnal events such as difficulty in falling asleep, multiple awakenings, sleep fragmentation, snoring can be retained. The consequences of these poor nights are also elements of attention: fatigue, irritability, excessive daytime sleepiness, and attention and memory problems (59). However, the consequences of SAS are particularly dramatic for the cardiovascular health of patients. They must therefore be diagnosed very early in order to be managed rapidly to avoid the development of pathologies that are deleterious to health and quality of life.

The diagnosis of SAS can only be established after a rigorous clinical investigation, based on several diagnostic elements (questionnaires, polysomnography…). Treatment then usually consists of the use of a continuous positive airway pressure (CPAP) machine during sleep (60). This treatment is sometimes very restrictive for the patient and therefore poorly tolerated. Today, one of the proposals made in T21, when the AHI is not severe and the patient refuses to use devices at night, is based on a physical activity program associated with the implementation of strict hygienic and dietary measures.

Interest in the effects of physical activity for populations with cognitive disabilities is a relatively recent topic. Physical activity has been proposed for about a decade as a non-pharmacological interventional method that has many benefits for children with disabilities and sleep disorders. However, offering physical activity to these populations must also be done within a rigorous and safe framework in order not to induce additional deleterious effects.

4. Physical activity and Down syndrome

Physical Activity is defined as the movement of the human body that requires energy expenditure (61). It is considered an effective, non-pharmacological approach to improving sleep. The scientific literature on the links between sleep and physical activity is now particularly rich and the consensus on the bi-directional links between sleep and physical activity is also well demonstrated (Figure 2). Healthy sleep of sufficient quality and quantity contributes to better physical performance and conversely regular physical activity improves sleep (62, 63). However, physical activity is considered to have positive effects on sleep quality if indeed the adjustment of factors such as level, intensity and duration of exercise is adequate (64). For example, significant improvements in sleep efficiency, sleep latency, sleep duration, and nocturnal

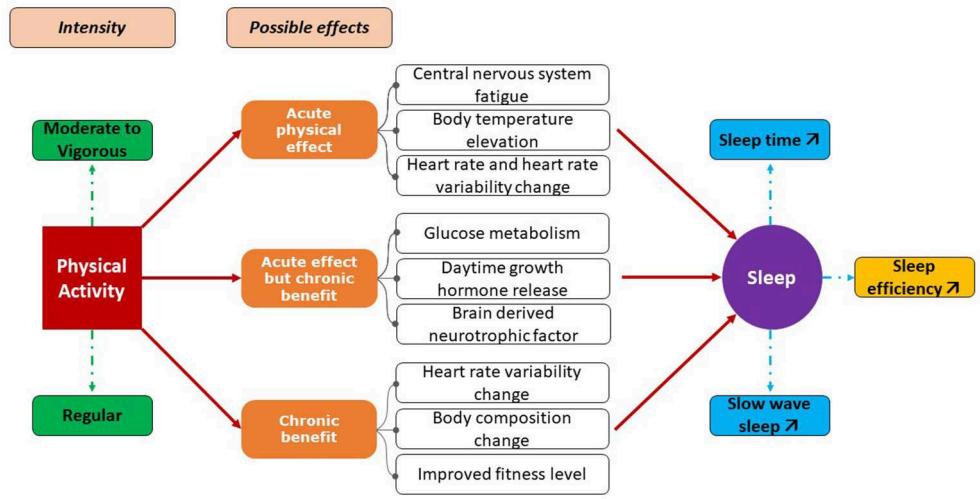

FIGURE 2
Positive effects of physical activity on sleep.

wakefulness times are reported when physical activity is increased and controlled (64).

The benefit of PA in the management of SAS for the population with Down syndrome has been demonstrated (65, 66). PA not only reduces the severity of SAS but also improves autonomic function through decreased sympathetic tone (67). Some studies have also reported positive effects of regular physical activity on physiological responses to stress (38), weight loss, and cardiovascular responses to exercise (68–70).

However, some anatomical peculiarities of T21, described previously, may limit the ability to perform certain types of effort, and at the same time explain the prevalence of SAS in this population. Many malformations (macroglossia, glossoptosis, narrow upper airways) that are well described in the responsibility of obstructive apneas, limit ventilatory exchange during physical activity (71).

Although PA has clear benefits in limiting the health consequences of SAS in T21 and non-T21 patients with Down syndrome, there are a variety of factors that not only contribute to worsening the consequences of SAS, but also act as barriers to the management of these sleep disorders.

The practice of PA is not yet offered in all establishments that receive people with Down syndrome. The institutionalization of people with T21 and their drug treatments are factors that limit physical activity.

The cognitive characteristics of T21 (early aging, intellectual deficit, difficulties in understanding instructions, low motivation to practice) also constitute barriers to physical activity.

However, encouraging the practice of a regular physical activity is a major challenge. In this sense, several studies have shown that for young people with T21, group activities should be preferred (72, 73) which are more in line with the social character of people with T21. Several studies have shown the benefit of re-training programs in T21 with an improvement in physical fitness with benefits on aerobic capacity (74), cardiovascular function (69, 75), muscular strength, balance and motor function (76–80). Improving this fitness simultaneously contributes to a decrease in body fat (76–80).

Finally, the benefits of PA on cognitive abilities in individuals with T21 have also been widely described (81). The management of sleep apnea through physical activity in T21, helps to combat a sedentary lifestyle and reduce the risk factors associated with SAS (82). It also increases sleep duration and quality (77, 83–85). In order to improve the health and quality of life of individuals with T21, early interventions and physical activity recommendations should be offered to value a healthy lifestyle and improve understanding of the benefits on sleep quality and quantity.

5. Conclusion

Individuals with Down syndrome had adverse genetic, anatomical characteristics that increase the risk of sleep apnea and mobility limitations, meanwhile physical activity has been reported with positive effects on sleep quality through a significant reduction in the apnea-hypopnea index in this population in this population. However, we need to understand more about the relationship between quantity and level of physical activity on sleep quality to provide information and recommendations for the design the optimal physical activity programs for the Down syndrome community, thereby helping to improve their quality of life.

Author contributions

D-TN drafted the initial manuscript and revised the final manuscript. V-HP support to improve the manuscript after the review process. V-AB, H-TT, and SD-Q revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A wearable device for at-home obstructive sleep apnea assessment: State-of-the-art and research challenges

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In the last 3 years, almost all medical resources have been reserved for the screening and treatment of patients with coronavirus disease (COVID-19). Due to a shortage of medical staff and equipment, diagnosing sleep disorders, such as obstructive sleep apnea (OSA), has become more difficult than ever. In addition to being diagnosed using polysomnography at a hospital, people seem to pay more attention to alternative at-home OSA detection solutions. This study aims to review state-of-the-art assessment techniques for out-of-center detection of the main characteristics of OSA, such as sleep, cardiovascular function, oxygen balance and consumption, sleep position, breathing effort, respiratory function, and audio, as well as recent progress in the implementation of data acquisition and processing and machine learning techniques that support early detection of severe OSA levels.

KEYWORDS

OSA, SCOPER, machine learning, wearable device, COVID-19

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repeated interrupted upper airflow during sleep. Previous studies have reported that sleep disorders, such as OSA, are associated with heart disease (1), diabetes type 2 (2, 3), stroke (4, 5), and depression (6). Sleep apnea affects the quality of life and working performance and is associated with other diseases; however, it does not lead to death by stopping breathing. This may be why OSA is underestimated as not many people are aware of or diagnosed with it.

The prevalence of OSA has been rising and affecting all countries. An investigation by Benjafield AV presents a global prevalence and burden that OSA may cause (using AHI and AASM 2012 criteria), in which "936 million [95% confidence interval (CI) 903–970] adults aged 30–69 years (men and women) may have mild to severe OSA and 425 million (95% CI 399–450) adults aged 30–69 years may have moderate to severe OSA globally" (7). In Vietnam, ∼8.5% of adults, which is equivalent to ∼5.9 million persons, have an AHI of >15 (8), especially those with systemic hypertension and chronic obstructive pulmonary disease (9, 10).

Despite the negative impact of OSA on health and its increasing prevalence, poor awareness about OSA has been reported in many countries, such as Singapore (11), Saudi Arabia (12), Pakistan (13), and, unfortunately, even worse in mid-and low-income countries. Currently, polysomnography (PSG) is the gold standard for evaluating sleep apnea/hypopnea (14). PSG can record multiple parameters of a person, such as brain waves [electroencephalography (EEG)], nasal–oral airflow, thoracoabdominal effort, and snoring, within the 8 h sleeping at a hospital (Figure 1).

During the COVID-19 pandemic, almost all resources were reserved for testing, diagnosing, and treating patients with COVID. Hospitals did not have sufficient facilities or human resources for other diseases, even in emergencies. This has led to more people with OSA not being screened

and diagnosed, resulting in a long waiting queue of people who wish to meet the physician for a diagnosis at the laboratory. During the post-COVID period, countries prioritized some urgent diseases, such as cardiovascular diseases, cancers, hepatitis B, and dengue fever, which increased the number of OSA cases and the severity. This may be why people seem to be paying more attention to alternative home OSA detection solutions. Therefore, early diagnosis of OSA and suitable proposed therapies for patients have interested many companies.

This study aims to review the possible impact of the SARS-CoV-2 virus and OSA and summarize state-of-the-art assessment techniques for out-of-center detection of the main characteristics of OSA, such as sleep, cardiovascular function, oxygen balance and consumption, sleep position, breathing effort, respiratory function, and audio. The study also aims to review recent progress in the implementation of data acquisition and processing and machine learning techniques that support the early detection of severe OSA levels.

2. Association between COVID-19 and OSA

The SARS-CoV-2 virus causes the infectious COVID-19, which affects the respiratory system. It can cause lung complications; therefore, it affects the airflow of patients, particularly those with OSA which is usually characterized by upper airway obstruction at night.

Maas et al. evaluated 5,544,884 patient records, of which 9,405 were COVID-19-infected cases, to identify possible links between OSA and the risk of COVID-19 infection and the severity of the disease. The study found that among patients with COVID-19, ∼34% were hospitalized and 19% were diagnosed with respiratory failure. The prevalence of hospitalized patients with OSA was higher than that of those without OSA [15.3 vs. 3.4%, $p < 0.0001$; odds ratio (OR) 5.20, 95% CI (4.43, 6.12)]. A similar result was found regarding respiratory failure rate [OR, 1.98; 95% CI (1.65, 2.37)] (15).

Labarca et al. conducted a study of COVID-19-infected people (≥18 years of age) to determine the association of OSA with long-term symptoms and inflammatory cytokines (4 and 12 months after the COVID treatment). The OSA group demonstrated poor effects on insulin resistance levels, metabolic change, cytokine levels, and symptoms compared with the non-OSA group (16).

A study by Alemohammad et al. in 2021, conducted with 275 (adult) participants diagnosed with OSA, reported that pro-inflammatory characteristics of OSA may increase the risk of COVID-19, and severe OSA was associated with higher COVID-19 prevalence among patients with OSA (17).

The prevalence of SARS-CoV-2, being a respiratory disease virus, is thought to be associated with comorbid conditions, including age, male sex, hypertension, elevated body mass index/obesity, diabetes, and chronic obstructive lung disease. In addition, previous studies found that OSA was independently associated with an increased risk of developing severe COVID-19; however, OSA may be a risk factor for severe COVID-19 (18–20).

COVID-19 has not yet been completely controlled because it will take years for humans to fully understand and synthesize specific drugs for such a disease. Furthermore, much work should be done to improve OSA screening and achieve more effective treatment.

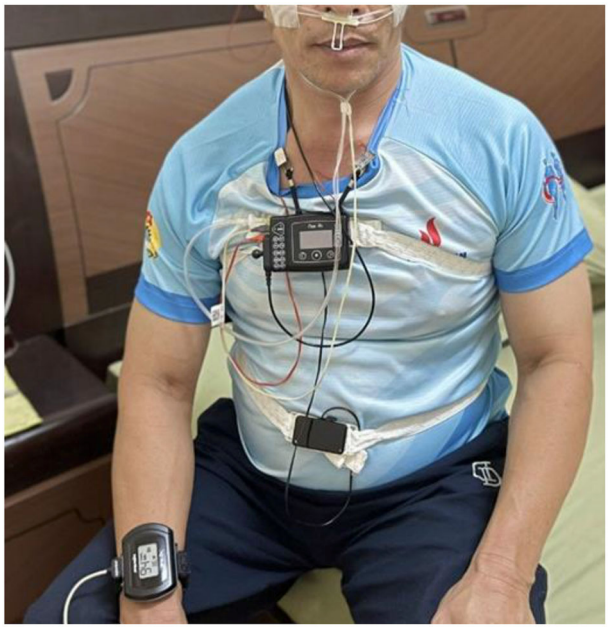

FIGURE 1
OSA patient is diagnosed using a multi-electrode PSG at a sleep laboratory.

3. Detection of main characteristics of OSA

The early diagnosis of OSA and the development of suitable therapies for patients have interested many companies. To date, PSG has been the gold standard for evaluating sleep apnea/hypopnea (14). PSG can record multiple parameters of a person, such as brain waves, nasal-oral airflow, thoracoabdominal effort, and snoring, within at least 8 h sleeping in a sleep laboratory. With the continuous support of a technician, sleep is continuously recorded, and other sleep conditions may be observed. However, the PSG test requires a person to go to a sleep laboratory and stay overnight for an entire test, which makes one feel uncomfortable and inconvenient. In addition, costly PSG will limit the number of patients tested, especially those in mid- and low-income countries. Therefore, the development of alternatives, such as out-of-center sleep tests, allowing a person to evaluate and predict a possible OSA at home [Home Sleep Testing (HST)] plays an important role and will help more people access such healthcare solutions and services.

Sleep studies in engineering, especially developing portable or wearable mobile devices for evaluating OSA at home, have received considerable attention from research groups worldwide. The studies in the literature focused on six main topics summarized as SCOPER

Abbreviations: AASM, American Association of Sleep Medicine; AHI, Apnea–hypopnea index; AI, Artificial intelligence; CNN, Convolutional neural network; ECG, Electrocardiogram; EEG, Electroencephalogram; EOG, Electroocoulogram; EMG, Electromyography; FFT, Fast Fourier transform; HST, Home Sleep Testing; KNN, K-nearest neighbor; LR, Logistic regression; OOC, Out-of-center; OSA, Obstructive sleep apnea; RF, Random forest; SVM, Support vector machine; PSG, Polysomnography; PCB, Printed circuit board; SpO2, Saturation of peripheral oxygen.

TABLE 1 Commercial HST devices.

Device	Company	Electrode	Data storage (GB)	Data recording time (hours)	Reference
Nox T3s	Nox Medical	Breathing effort, respiratory sound, gravity, position, flow, snore, PWA; pulse, SpO2; heart rate	4 built-in	24 with 1 AA battery	noxmedical.com
ApneaTrak Type 3 HSAT	Cadwell Industries Inc.	Thoracic/abdominal effort, snore sensor, thermistor, SpO2, pulse rate, body position.	0.1 built-in	18	cadwell.com/apneatrak
BWMini HST Compass	Neurovirtual USA Inc.	Effort, pressure transducer, SpO2, pulse, plethysmography, body position, luminosity sensor	3.2 built-in	12 with 1 AA battery	neurovirtual.com
Zmachine Synergy	General Sleep Corporation	EEG, respiratory effort (RIP), snore, SpO2, pulse rate, body position	8.0 built-in	300 with Lithium Ion 3.7 VDC	generalsleep.com
Somté	Compumedics USA	Nasal pressure, snoring, thoracic and abdominal effort, body position, SpO2, pulse rate, limb movement, EEG, EOG, EMG, ECG	Inserted card	36	compumedics.com
MediByte Jr	BRAEBON Medical	Airflow, snore, SpO2, pulse rate, chest effort, body position, CPAP pressure, PPG	0.2 built-in	18 with 1 AA battery	www2.braebon.com
Alice NightOne	Philips	Flow, snoring, thoracic effort, SpO2, heart rate, body position, plethysmogram.	0.4 built-in	10 with 1 AA battery	usa.philips.com
Cerebra Sleep System	Cerebra	Brain waves (EEG), Eye movements (EOG), Respiratory data, Pulse oximetry, Heart rate (ECG), Chin and leg activity (EMG), Body position, Snoring, Oxygen saturation (SpO2).	0.3 built-in	13 with 1 AA battery	cerebra.health

categorization (21): Sleep; Cardiovascular; Oximetry; Position; Effort; and Respiratory.

HST is an attractive alternative to PSG for insurance companies and patients because it is affordable. For a patient, having a sleep test at home is much more convenient than spending a whole night in a remote room and being monitored during sleep at a laboratory. In addition, with HST, one does not need to book a bed in the presence of a sleep technologist to monitor the sleep parameters.

This potential market for commercial HST devices has attracted many investors (Table 1). The HST devices are normal full-fill type II, III, and IV levels of sleep study, among which type II approaches full PSG measurements outside the laboratory. The main difference from type 1 devices is that the sleep study is performed without a medical technician. The HST device usually is built-in with an internal memory that allows 300 h data storage with a disposable or rechargeable battery. The weight of the HST device (including the battery) does not exceed 350 g. In addition, the user (patient or medical doctor) can refer to the test results at home (Table 1).

In the research and development phase, many research groups study SCOPER parameters to introduce more products to manufacturers, focusing on reducing the number of sensors and improving measurement accuracy.

Sleep parameters can be studied using electrooculography (EOG), EEG, and electromyography (EMG) to acquire sleep data. The sensors can be placed on the scalp, the forehead, the ear, or the chest (22–25).

Shustak et al. proposed an ambitious project for an in-home OSA detection system using temporary-tattoo EEG, EOG, and EMG electrode arrays (26). They demonstrated that a polyurethane film-based electrode array allowed for the simultaneous monitoring of EMG, EOG, and EEG signals during napping and night sleep. The electrode array was interfaced with a built-in low-energy Bluetooth and an Intan SoC PCB for data collection and processing.

A simple configuration of microphones (Earthworks M23, Behringer ECM8000) was used to record snoring sounds during sleep using a combination of a convolutional neural network (CNN) and a recurrent neural network (RNN), as reported by Xi Long et al. Overall, accuracy of 95.3 $\pm$ 0.5%, sensitivity of 92.2 $\pm$ 0.9%, and specificity of 97.7 $\pm$ 0.4% were obtained in the study (27).

OSA can be studied by combining multiple approaches, such as an electrocardiogram (ECG), EEG, and sPO2. Each approach demonstrated the possibility of developing advanced devices for OSA detection.

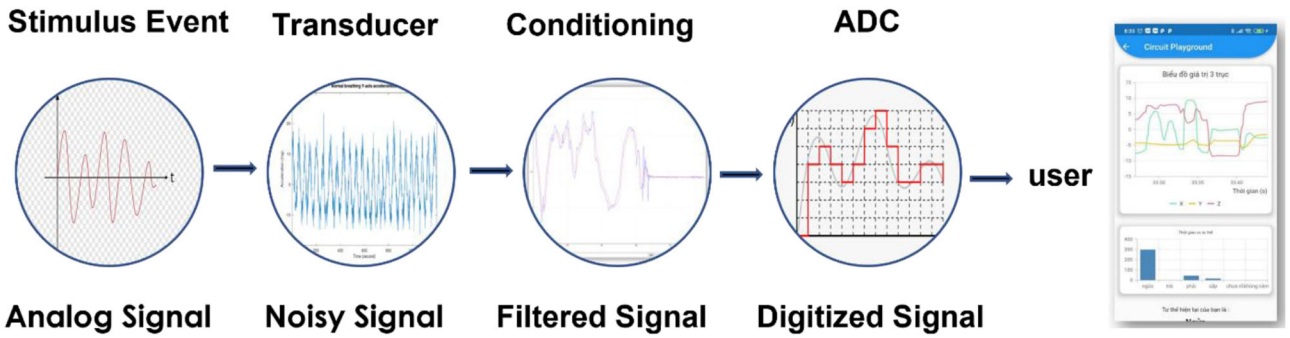

FIGURE 2
A signal is detected by a transducer and converted into digital form, processed, and displayed on a user interface.

4. Data acquisition and processing

In general, a non-electric stimulus signal is converted into an electrical signal by a transducer in analogic form, which is then transformed into digital form using an ADC and finally to analogic form again, enabling the user to see the result of the measurement (Figure 2). However, the input data are disturbed by existing noise in the measuring environment.

The signal-to-noise ratio can be improved using both hardware and software. For example, in a sleep apnea study, one should select the frequency range in which the data will be collected, and naturally, the out-of-range ones are filtered out. As a result, the developer will probably define the specific characteristics of the selected sensors for specific purposes (Table 2). Furthermore, selecting suitable sensors characterized within a limited time will also be effective for the calibration step.

In addition to the hardware approach, the Fast Fourier Transform (FFT), a means of mapping a signal, either in the time or space domain, to its spectrum in the frequency domain, is usually utilized in sleep apnea studies. FFT allows the computation of discrete Fourier transform (DFT) of a sequence with high efficiency. Therefore, the system may require less performance hardware and significantly reduce computation time. For example, Belhaouari et al. implemented an ECG using FFT to diagnose sleep apnea with 100% accuracy (36). In addition, overnight breath recording data were collected, conditioned by the FFT, and learned using random forest (RF) and support vector machine (SVM), which offer an overall accuracy of >90% (37).

The sleep stage was evaluated using brainwave signals from EEG and FFT to improve accuracy (~96.54%), and the performance of automated sleep classification was reported by Delimayanti et al. (38). FFT can also monitor non-invasive respiration using ECG-derived respiratory (EDR) signals. A combination of FFT preprocessing, linear and quadratic Discriminant (LD and QD) models, K-nearest neighbor classifiers (KNN), SVM, and an artificial neural network (ANN) offered an evaluation with 100% accuracy (39).

The acquired and processed data can be deposited on the cloud using various options. For example, the developer can either select private or public, free or paid, or hybrid clouds from different providers such as Amazon, Google, Microsoft, Alibaba, Oracle, IBM, Digital Ocean, and Dropbox (Figure 3).

5. Machine learning in OSA study

The wearable device has fewer sensors for at-home sleep apnea detection than the HST (commercially available). In addition, machine learning and artificial intelligence (AI) are used after data processing to improve the accuracy and precision of the measurement.

RF, SVM, Logistics Progression, and Naive Bayes classifier are the models typically used in sleep studies. Each model may be suitable for one or two different signal types. For example, regularized logistic regression (LR) appears faster for tracheal breathing sounds than RF. In contrast, RF seems better than LR in blind-testing accuracy, specificity, and sensitivity; therefore, both are good for OSA research (40).

Álvarez et al. conducted research with 303 patients with OSA on adult sleep apnea screening for >2 years at home using airflow and SpO2 sensors. The study implemented SVM as a machine-learning model and showed that the accuracy was >95% using both SpO2 and airflow data (41).

Usually, a sleep study involves more than one machine learning model to improve accuracy, specificity, and sensitivity. For example, Gallo et al. implemented ML, KNN, RT, SVM-R, LR, and Adaboost in their research to determine the optimal one in an OSA study (42). In the study by Wu et al., RF, KNN, and SVM classifiers were used to classify sleep apnea using EEG signals with an average accuracy rate of 88.99% after 10-fold cross-validation (43).

Research groups have implemented deep learning in OSA studies. Deep learning is a particular type of machine learning that can handle different types of data, such as images, videos, and raw data. Deep learning processes a large dataset. This requires more computing power than human intervention.

Yue et al. reported the multi-resolution residual network (Mr-ResNet) detecting nasal pressure airflow signals from a PGS at sleep laboratories. According to the authors, the Spearman correlation for AHI between the obstructive sleep apnea smart system (proposed by the research group) and the registered polysomnographic technologist score was 0.94 ($p < 0.001$) and 0.96 ($p < 0.001$), respectively. Furthermore, Cohen's kappa scores for classification obtained by the two technologists were 0.81 and 0.84, respectively (44).

The 1D CNN model was used in the study by Lin et al. to develop a sleep apnea system. The proposed model was composed of 10

TABLE 2 Frequency range and selected sensors used in sleep apnea.

Sensor	Measurement	Range	Reference
Accelerator	Wake and sleep periods	0.1 Hz−0.4 Hz	(28)
Acoustic sensor	Respiratory sounds	100–1,400 Hz	(29)
Acoustic sensor	Tracheal sound	100–3,000 Hz	(30)
Acoustic sensor	Sound transmission in respiratory system	150–500 Hz	(31)
Pressure sensor	Pressure	0.06–1.7 Hz	(32)
Captive microphone	Respiratory sound	30–126 Hz	(33)
Captive microphone	Respiratory sound	20–6,000 Hz	(34)
Acceleration sensor	Actigraphy, body position	1–4 Hz	(35)

identical CNN-based feature extraction layers, one flattened layer, four identical classification layers, and a softmax classification layer. The ECG data were extracted from two sleep laboratories to train the model. For the per-recording classification, the accuracy was 97.1%, specificity was 100%, and sensitivity was 95.7% (45).

Recent research reported by Nguyen et al. demonstrated a head-based sleep-aid system for promoting fast falling into sleep and improving the accuracy of sleep tracking. Using a multi-sensor configuration (accelerator, PPG sensor, and bioelectrodes) for EEG, EOG, sleep posture, breathing, and heart rate, the author implemented a set of algorithms to achieve great agreement with results obtained by a PSG (46).

6. Discussion

Home OSA assessment has many advantages; however, some challenges must be overcome to make such alternative solutions more popular and accepted by patients, physicians, and medical insurance companies.

Existing out-of-center OSA assessment devices employ fewer components than a PSG; however, they still have complicated moving parts that may not be convenient for patients with backgrounds such as chronic obstructive pulmonary disease, congestive heart failure, and neuromuscular diseases. In addition, to our knowledge, the average price of an HST device is >2,500 USD. However, a patient can sometimes hire an HST device for ∼300 USD per night.

6.1. Challenges for HST development

HST, as discussed earlier, has many advantages for patients; however, there are challenges that solution and product developers must overcome to make such testing methods more prevalent for patients, physicians, and medical insurance companies. A review of the literature reveals the following key challenges for device developers.

6.1.1. Accuracy improvement

HST uses less hardware on board; therefore, assessments may miss important information about OSA. HST does not record sleep, but only breathing and/or a stop in breathing; therefore, the accuracy needs to be improved by combining two or three sensors on a board. Accuracy can be improved by implementing suitable machines and deep learning techniques.

6.1.2. Limit of the tested population

Existing HST devices employ fewer components than PSG; however, they still have complicated moving parts such as pumps, electrodes, and control panels. Such a configuration may not be suitable for patients with chronic obstructive pulmonary disease, congestive heart failure, or neuromuscular disease. For the patient's convenience, the system configuration must be simpler and more comfortable. Two or three types of sensors on a small board may be sufficient to collect two or three types of signals associated with OSA characteristics.

6.1.3. Collaboration with physicians

To date, most studies on system development, including devices and software, for OSA detection and diagnosis have been reported by technical teams; however, technology and solutions must be reviewed and revised by physicians from sleep laboratories. A loose collaboration with physicians may lead to the number of samples (tested participants) not being large enough for a sustainable evaluation of the device and solution. The strong support of physicians will guide the engineering team in the right and shortest path for medical equipment that patients will accept. In addition, this support can help increase the number of tested participants according to different variants (age, sex, or medical history compatible with existing solutions and services) to improve the accuracy of the algorithms and machine learning techniques.

6.2. The trend in OSA device development

The trend in developing mobile devices for OSA detection is a smart combination of a simple hardware configuration that integrates two or three kinds of sensors on a small PCB. Suitable data acquisition and processing should be applied

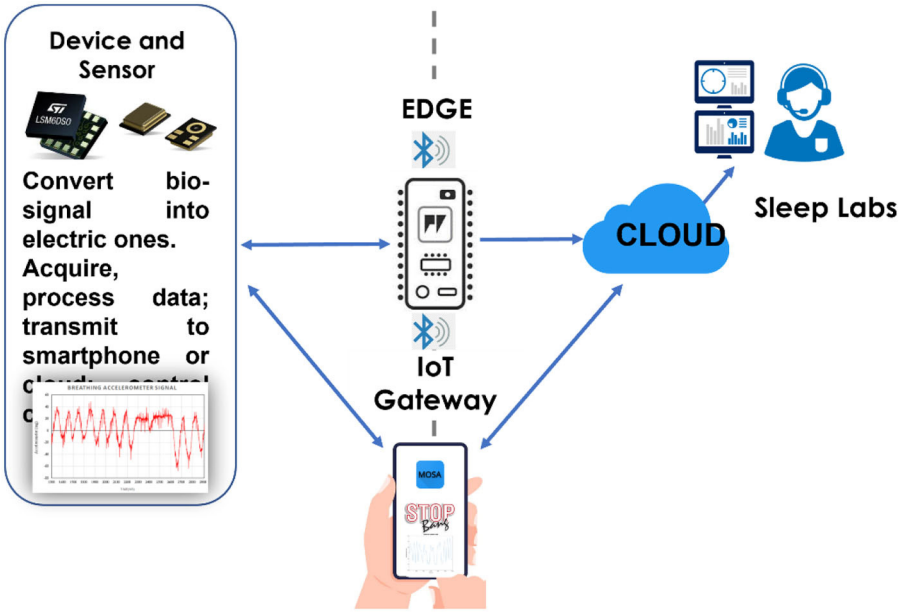

FIGURE 3
The data can be deposited on a service cloud.

to remove artifacts and enhance the signal-to-noise ratio. Furthermore, the data of a study should be sufficiently large to implement machine or deep learning models and to enhance the accuracy, sensitivity, specificity, and precision. Importantly, data mining should be conducted in a case–control study using the PSG method.

Data processing and storage appear to benefit from the development of the information and electronics industries. Advanced battery technology allows a wearable sleep-testing device to operate for 10 h or more with a compact rechargeable lithium-ion polymer battery. Developers can also choose wire or wireless charging modes for their solution. The cutting-edge technology with Bluetooth Ultra Low Energy and nano-range energy consumption integrated circuits and sensors make it possible for the device to work a whole night without recharging. Machine learning models can run on a Chip, Edge Device, or Service Cloud.

7. Conclusion

Today, digital transformation in healthcare is taking advantage of cutting-edge technologies and innovations to deliver sustainable service and medical solutions to patients, medical staff, and healthcare bodies. Home sleep apnea test (HSAT) is a promising and alternative sleep study solution for people with OSA that may help to save time and money while enabling improved interaction between physicians and patients. HSAT involves almost all major digital transformation trends in healthcare including health wearables, AI screening, disease history analysis, e-doctor, and data aggregation. However, to popularize such an advanced solution to one-seventh of the world's adult population (~1 billion people, especially people in mid- and low-income countries), great efforts of the developers, medical staff, patients should be made to simplify the hardware with a smaller number of sensors, to improve the accuracy of the test, to use with ease, and to reduce the service cost of the solution.

Author contributions

AM: conceptualized, validated, and wrote the original draft. AM, NT, and HT: methodology and writing review. All authors have contributed to the manuscript and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Benchmarking performance of an automatic polysomnography scoring system in a population with suspected sleep disorders

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Aim: The current gold standard for measuring sleep disorders is polysomnography (PSG), which is manually scored by a sleep technologist. Scoring a PSG is time-consuming and tedious, with substantial inter-rater variability. A deep-learning-based sleep analysis software module can perform autoscoring of PSG. The primary objective of the study is to validate the accuracy and reliability of the autoscoring software. The secondary objective is to measure workflow improvements in terms of time and cost *via* a time motion study.

Methodology: The performance of an automatic PSG scoring software was benchmarked against the performance of two independent sleep technologists on PSG data collected from patients with suspected sleep disorders. The technologists at the hospital clinic and a third-party scoring company scored the PSG records independently. The scores were then compared between the technologists and the automatic scoring system. An observational study was also performed where the time taken for sleep technologists at the hospital clinic to manually score PSGs was tracked, along with the time taken by the automatic scoring software to assess for potential time savings.

Results: Pearson's correlation between the manually scored apnea–hypopnea index (AHI) and the automatically scored AHI was 0.962, demonstrating a near-perfect agreement. The autoscoring system demonstrated similar results in sleep staging. The agreement between automatic staging and manual scoring was higher in terms of accuracy and Cohen's kappa than the agreement between experts. The autoscoring system took an average of 42.7 s to score each record compared with 4,243 s for manual scoring. Following a manual review of the auto scores, an average time savings of 38.6 min per PSG was observed, amounting to 0.25 full-time equivalent (FTE) savings per year.

Conclusion: The findings indicate a potential for a reduction in the burden of manual scoring of PSGs by sleep technologists and may be of operational significance for sleep laboratories in the healthcare setting.

KEYWORDS

automatic sleep scoring, sleep-disordered breathing, machine learning, AI sleep scoring, sleep staging

1. Introduction

An estimated 50–70 million people in the US have a sleep disorder (1). Economic modeling of five OECD countries estimated the economic loss due to sleep loss to be up to 3% of GDP (2). Polysomnography (PSG) remains the gold standard for measuring sleep. The medical procedure involves concurrent measurement of multiple physiological signals comprising of electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), nasal pressure, airflow, thoracic and abdominal movement, and blood oxygen saturation, among others. Following data collection, the sleep technologist spends ∼1–2 h manually scoring the record as per standardized criteria. The most widely adopted criteria are established by the American Academy of Sleep Medicine (AASM), which are updated regularly (3–6).

The process of scoring can be broadly divided into two major tasks: sleep staging and detection of associated respiratory events. Staging involves the division of the record into 30-s epochs and assigning one of the five sleep stages (Wake, N1, N2, N3, and REM) based on patterns in the EEG/EOG/EMG channels. This is followed by identification of various events across different channels. This includes identification of oxygen desaturation events, arousals, apneas, hypopneas, and periodic leg movements. Wherein apneas can be further categorized into obstructive, mixed, and central, and arousals can be categorized into spontaneous, respiratory, or limb movement related. The process is time-consuming and requires strong expertise and consistent attention for reliable results. Although the scoring criteria are standardized, the process remains highly subjective, which introduces significant inter-rater variability (7–11). A meta-analysis of 11 studies found an average agreement for sleep staging at Cohen's kappa of 0.76, indicating substantial agreement (8). The agreement varied greatly across different sleep stages, with the lowest average kappa of 0.24 for N1 and the highest kappa of 0.70 for wake. Although inattention and bias play a role in disagreements, most of the variability in sleep staging is attributed to the fact that many epochs legitimately do not have a clear classification (12). With regard to primary respiratory outcomes like the apnea–hypopnea index (AHI) or oxygen desaturation index (ODI), the agreement among raters is excellent (9). However, the agreement across specific respiratory events can be low (9, 11). Specifically, disagreements between apnea and hypopnea and the types of apneas are common (11).

Therefore, automatic scoring can play a significant role in reducing the burden on sleep technologists while simultaneously reducing variability in scoring. In this study, we benchmark the performance of an automatic scoring system called Neurobit PSG (Neurobit Inc., New York, USA). Neurobit PSG uses deep-learning (DL)-based algorithms to stage sleep and a combination of DL and rule-based systems to identify respiratory events. By default, it scores as per the 2012 AASM standard (3) but is flexible to accommodate popular alternate standards. To establish the viability of such a system, it is important to compare the level of agreement between automatic scoring and experts to an agreement between experts. In addition, productivity gains through the use of the system can also be established.

2. Materials and methods

2.1. The sleep scoring system—Training dataset

The sleep scoring system called *Neurobit PSG* was developed by Neurobit Inc., New York, NY, USA. The system uses DL-based architecture to provide sleep staging and detection of associated respiratory events. The system was trained and tested on private datasets comprising 12,404 PSG recordings collected at academic sleep centers in South-East Asia (35%), North America (30%), and Europe (30%). In all, 59% of the total assessed participants had a suspected sleep disorder, whereas the remaining 41% of participants were healthy subjects. The mean age of such aggregated dataset was 42.3 ± 16.8 (mean ± std) years. The training data were scored as per the 2007 AASM standards or higher. The software is designed to operate on two EEG channels C3-A2 and C4-A1; two EOG channels E2-A2 and E1-A2; and a bipolar EMG channel for staging. Alternate EOG derivations referenced to A1 or a mix of A1 or A2 are also acceptable by the software. SpO_2 channel is used for desaturation. Airflow, Pressure, Thoracic, and Abdominal channels are used for the detection of respiratory events. The selection of input channels was made based on common channels available across the complete training dataset. As per the AASM standards (5), the C4-A1 channel and its backup channel C3-A2 are present in both the recommended and alternate EEG derivations. For EOG channels, AASM recommends derivations referenced to A2, but derivation referenced to A1 is also acceptable. The software is designed to automatically handle electrode fall off, noisy, or missing channels.

2.2. Subjects

Overnight, in-laboratory PSG recordings from adult patients referred to the clinical sleep laboratory at Changi General Hospital, Singapore, with suspected organic and functional sleep disorders were included in the study. The scoring software was never trained or tested on data from the sleep laboratory before. The study was approved by the Singhealth Centralized Institutional Review Board (CIRB Ref. 2020/2000).

A total of 94 subjects participated in the study. Data from the first five subjects were used to ensure that the software was installed and integrated properly at the clinic. These records were not considered for further analysis. Finally, data from 86 subjects (18 women and 68 men) were included in the comparative analysis. The set was composed of ∼67.4% Chinese, 20.9% Malay, 9.3% Indians, and 2.3% other races, which is representative of the Singaporean population. Notably, 31.4% of the subjects had hypertension, 17.4% had diabetes, 1.2% had chronic obstructive pulmonary disease, 25.6% had hyperlipidemia, 4.7% had ischemic heart disease, 10.5% had asthma, and 4.7% had depression. The mean age of the subjects was 44.0 ± 14.4 (range 14–75) years. Further clinical profiling of patients can be found in Table 1.

TABLE 1 Clinical and demographic characteristics of patients in dataset.

Demographic/clinical characteristics	Mean ± SD or *N* (%)	Min	Max
Age (years)	44.0 ± 14.4	14	75
Men	68 (79.1)	–	–
Race Chinese Malay Indian Others	 58 (67.4) 18 (20.9) 8 (9.3) 2 (2.3)	–	–
BMI (kg/m^2)	30.9 ± 7.6	18.6	65.4
AHI total (events/h)	35.3 ± 32.6	0.3	134
REM AHI (events/h)	35.2 ± 29.5	0	114.8
NREM AHI (events/h)	34.8 ± 33.7	0.2	135.8
Supine AHI (events/h)	39.8 ± 33.9	0	134
Non supine AHI (events/h)	21.6 ± 31.5	0	138.5
ODI (events/h)	28.1 ± 30.1	0	108.8
% TST SPO_2 < 90%	9.8 ± 19.7	0	87.4
Arousal index (events/h)	29.5 ± 24.0	4.5	107

2.3. Protocol

Recordings were done on a Compumedics (Melbourne, Australia) PSG recorder. Recording signals included EEG channels: C4-A1, C3-A2, F4-A1, F3-A2, O2-A1, and O1-A2; EOG channels: E2-A2 and E1-A2; EMG channels: bipolar EMG, and Left and Right Leg EMG channels; and single ECG channel all sampled at 256 Hz. Respiratory channels, namely, Airflow, Pressure, Thoracic, and Abdominal channels sampled at 32 Hz. Arterial oxyhemoglobin saturation (SpO_2) was sampled at 16 Hz. The recording montage was based on recommendations of the AASM (3). The signals were stored, viewed, and analyzed using the Compumedics Profusion software version 4.0.

The records were scored manually by a group of trained Registered Polysomnographic Technologist (RPSGT) at the hospital as per the 2012 AASM guidelines (3). Each record was scored by one of the five technologists. For the sake of simplicity, we refer to the group of technologists as "**expert 1.**" The scoring was done visually within the Compumedics Profusion software. Specifically, for sleep staging, 30-s epochs were assigned one of the five stages (Wake, N1, N2, N3, REM) based on patterns in the EEG/EOG/chin EMG channels. Apneas were identified if there was a 90% or more reduction in airflow for at least 10 s compared with the baseline. For hypopnea, the criteria were set as a drop in thoracoabdominal movement or airflow drop of 30% or more compared with baseline for at least 10 s with at least 3% desaturation or an associated EEG arousal. Arousals were scored if there was an abrupt shift in EEG power lasting at least 3 s. The raw PSG data were also exported to European Data Format (EDF) (13), an open standard for the exchange of physiological data. The records were anonymized during export. These exported data were then securely sent to a third-party independent scoring company MBS Sleep Scoring Services, LLC (St. Louis, MI, USA) where it was scored by an RPSGT (**expert 2**). The technologist used the Philips Sleepware G3 (Philips Respironics, Inc., PA, USA) software to view and score the data manually as per the same 2012 AASM standards (3).

For automatic scoring (**auto**), an on-premise version of Neurobit PSG was installed at the hospital. This was necessary because the hospital did not have access to the internet in compliance with local security guidelines. The exported EDF files were transferred to the local machine using a secure thumb drive where they were auto-scored, and the results were generated in a Profusion compatible XML format. The scores were then transferred back to the Profusion software for review by the technologists. The local version of Neurobit PSG was installed in a *headless* mode, i.e., there was no user interface. As soon as EDF files were placed in a designated folder, the scoring started automatically based on the preconfigured montage, and the results were generated in the same folder. The only visual indication provided was an external LED cube that flashed when scoring was in progress.

2.3.1. Manual review of automatic scores

Automated scoring systems are expected to be used in conjunction with expert review to achieve high levels of reliability. Based on the performance and limitations of the automatic system, a manual review can be optimized to ensure excellent reliability while minimizing the time required to review. To avoid introducing systematic bias into the review process, experts from the clinic (expert 1) were instructed to review the automatic scores thoroughly. The reviewed scores (**review**) were then compared with automatic scores as well as the other expert scores to come up with an optimal strategy to maximize the throughput of scoring while maintaining a high degree of scoring accuracy and reliability. The time taken by expert 1 to manually score as well as to review the automatic scores was also logged.

2.3.2. Time motion study

Hired research assistants (RAs) were deployed at the sleep laboratory to observe and track the time spent explicitly by sleep technologists (expert 1) in order to complete the manual scoring of sampled PSGs. The RAs made sure that their presence did not distract the technologists in their day-to-day activities. RAs were required to differentiate tasks undertaken by the sleep technologists (expert 1) according to whether these tasks were related to scoring of PSGs (e.g., answering phone calls, going to toilets, and addressing queries by colleagues). The same set of sampled PSGs was then automatically scored by the automated scoring system (auto), and the amount of time spent autoscoring every PSG along with the additional time spent by the sleep technician to manually review the auto-scored PSGs were tracked by the RAs.

2.4. Data analysis

2.4.1. Statistical analysis

In the presence of significant variability in scoring between experts, it is difficult to determine what should be considered the ground truth. Instead of comparing the automatic scores with a single expert, it is, therefore, important to compare the automatic scores with multiple experts and stack them against the agreement between the experts. Ideally, the agreement between automatic and

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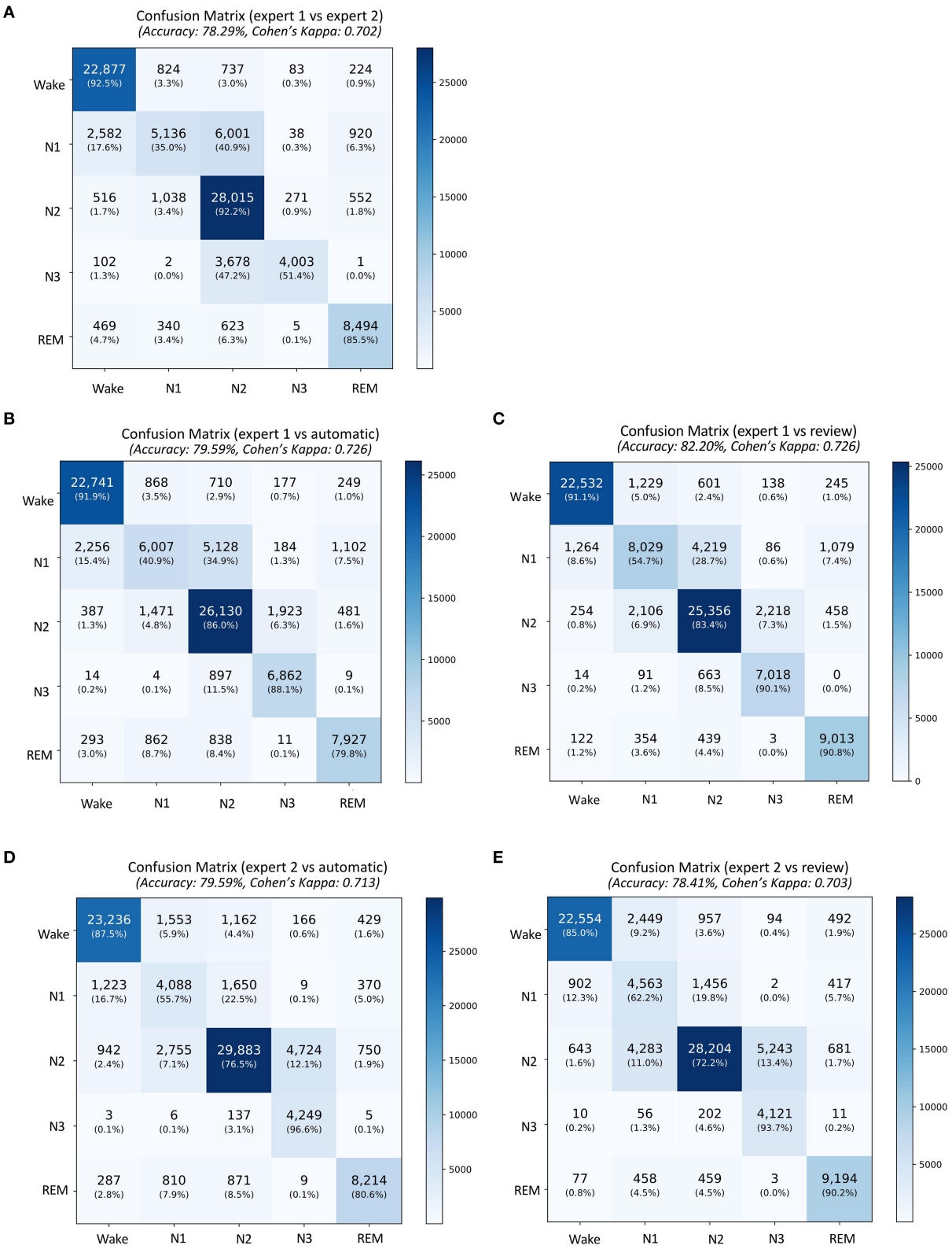

FIGURE 1
Confusion matrix comparing sleep stages between **(A)** the expert 1 (rows) and expert 2 (columns), **(B)** expert 1 and automatic staging, **(C)** expert 1 and review of the automatic scores by expert 1, **(D)** expert 2 and automatic staging, and **(E)** expert 2 and review of the automatic scores by expert 1. The confusion table is constructed by combining sleep stages across all subjects.

experts should be indistinguishable from an agreement between experts. In the study, we use accuracy, Cohen's kappa (κ) and intra-class correlation coefficient (ICC) to compare scores between experts and automatic scoring. Accuracy quantifies the agreement

between two raters, but it has been used as a simple measure of inter-rater reliability (IRR) (14). Cohen's kappa and ICC are appropriate measures of IRR. The IRR between experts provides an upper bound for the automatic scoring performance.

2.4.2. Sleep staging performance

For comparing sleep stages, an epoch-by-epoch comparison was carried out between auto, expert 1, and expert 2. This was done by combining all epochs across all subjects. A confusion matrix was calculated along with overall accuracy and Cohen's kappa. Cohen's kappa is considered to be a robust measure for IRR as it accounts for agreement due to random chance (14). The kappa statistic varies between −1 and 1, with values appaindicating no agreement and 0.01–0.20 as none to slight agreement, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement. To quantify the stage-specific agreement, kappa was also computed for each stage across expert–expert and expert–auto comparisons. A similar comparison was also carried out between auto and the concordance between the two experts. This was computed by only considering epochs where both the experts agreed with each other. To carry out the statistical comparison, subject-wise accuracy and kappa were also calculated. A one-way repeated-measures ANOVA was carried out to test if mean agreement between experts and between expert and auto was statistically different.

In addition to epoch-by-epoch comparison, derived sleep measurements were also compared between experts and auto. Specifically, total sleep time (TST), sleep efficiency, and time spent (both absolute and percentage of TST) in N1, N2, N3, REM, sleep latency, and REM latency were derived for every subject for each rater. Agreement between the raters was accessed through ICC (15). Based on the 95% confidence interval (CI) of the ICC estimate, values <0.5, between 0.5 and 0.75, between 0.75 and 0.9, and >0.90 are indicative of poor, moderate, good, and excellent reliability, respectively (15).

2.4.3. Detection of respiratory events

Respiratory events included apneas, hypopneas, arousals, and oxygen desaturation. Apneas were further subcategorized into central, mixed, and obstructive apneas. For each subject, the number of events were counted and compared across raters. Agreement between the raters was accessed through ICC (15). A comparison was also carried out between the auto and the average of the two experts. Indices were calculated by dividing the event count by TST. This included AHI and ODI. For AHI and ODI, which are the primary respiratory outcomes, Pearson's correlation with expert estimates was also obtained.

2.4.4. Time motion study

Manual scoring of trained experts at the hospital (**expert 1**) was compared against automatic scoring coupled with the additional time taken by the sleep technologists to manually review the automated scores generated using the software (**auto**). The paired *t*-test was used to assess the time difference between manual and automated scoring. The time saved with the use of automated scoring was used to estimate manpower FTE savings with the use of automated sleep scoring in our healthcare setting.

TABLE 2 Table comparing stage-wise agreement in terms of Cohen's kappa between experts and between each expert and automatic scoring.

	Wake	N1	N2	N3	REM
Expert1 vs. expert 2	0.847	0.399	0.683	0.633	0.824
Expert 1 vs. automatic	0.862	0.429	0.709	0.790	0.780
Expert2 vs. automatic	0.843	0.442	0.696	0.600	0.800
Expert vs. automatic (mean)	0.853	0.436	0.703	0.695	0.790

The mean agreement between automatic scoring and the two experts are computed in the final row.

2.4.5. Sample size calculation

The anticipated mean timing for manual scoring of a PSG is 45 min (SD = 10) and automated scoring at 40 min. Assuming α (type 1 error) = 0.05, β (type 2 error) = 0.9, and a group allocation ratio of 1:1, the sample size required for this analysis would be 168 patients, with 84 patients in the manual and autoscoring groups each. As both the manual and autoscoring were performed on the same patient, the sample size required would be halved at 84 patients.

3. Results

A total of 87,531 epochs (729.4 h) were compared between the experts and the auto. The confusion matrix is presented in Figure 1. The overall agreement between the two experts (Figure 1A) was 78.29%, with κ of 0.702 indicating substantial agreement. The overall agreement between expert 1 and auto (Figure 1B) was 79.59% with κ 0.726 and between expert 2 and auto (Figure 1D) was 79.59% with κ 0.713, again indicating substantial agreement. In absolute terms, the agreement between auto and the experts was higher than between both the experts for both accuracy and kappa. For individual sleep stages, the results are summarized in Table 2. The agreement was highest for wake (κ = 0.847 between experts vs. κ =0.853 between expert and auto), followed by REM (κ = 0.824 between experts vs. κ =0.790 between expert and auto), N2 (κ = 0.683 between experts vs. κ =0.703 between expert and auto), N3 (κ = 0.633 between experts vs. κ =0.695 between expert and auto), and finally N1 (κ = 0.399 between experts vs. κ =0.436 between expert and auto). Agreement between auto and the concordance of the two experts was 89.38%, with κ 0.850 indicating almost perfect agreement (Figure 2B). Between the two experts, the highest agreement was obtained for wake and REM sleep, while N3 and N1 sleep showed the least agreement, respectively (Table 2). A similar trend was also observed between expert and auto scores.

To statistically compare the staging agreement, subject-wise accuracy and kappa were plotted (Figure 3). The box plot indicated a few outliers for which the accuracy and corresponding kappa were very low. It was also observed that few records had very low kappa while still having high accuracy. On closer inspection, these records were dominated by one or two stages, while other stages were completely missing. In such scenarios, kappa measure can

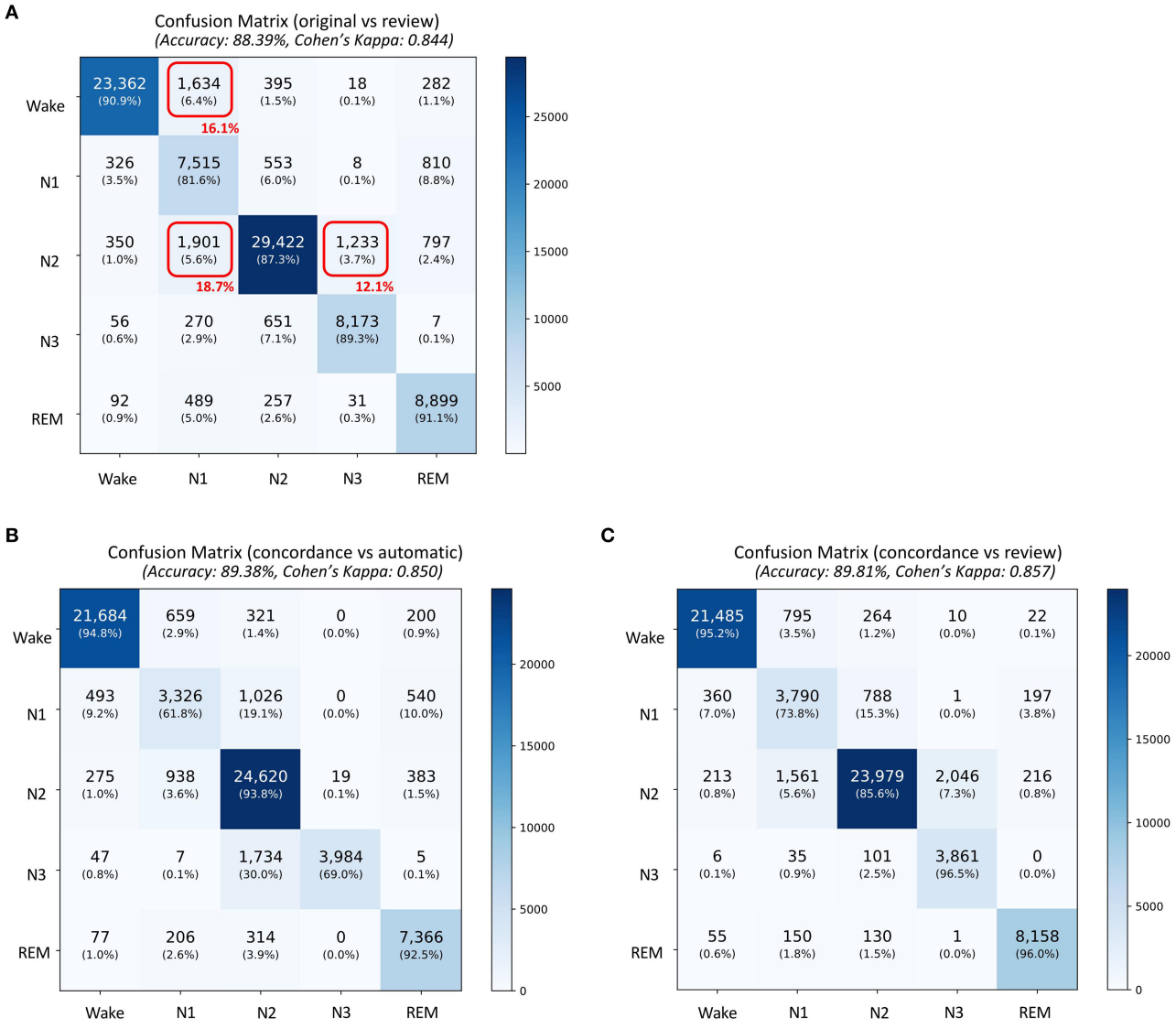

FIGURE 2
Confusion matrix comparing sleep stages between **(A)** the original scores generated by automatic algorithm (rows) and automatic scores obtained after review (columns), **(B)** concordance of the two experts and automatic staging (for concordant epochs), and **(C)** concordance of the two experts and automatic staging after review (for concordant epochs. The confusion table is constructed by combining sleep stages across all subjects. The red boxes in **(A)** indicate the three largest changes made after review. The numbers in red indicate percentage of total changes made during the review.

be low, even when accuracy is high. The average and aggregate accuracy and kappa are presented in Table 3. The average agreement between the two experts was 78.08 ± 11.70% with κ of 0.673 ± 0.172. Agreement between expert 1 and expert 2 with auto were 79.38 ± 11.08% with κ 0.695 ± 0.172 and 79.52 ± 9.82% with κ of 0.680 ± 0.158. Similar to the combined agreements, subject-wise average accuracy and kappa were higher between auto and experts as compared with between the experts. However, a one-way repeated-measures ANOVA did not detect any statistically significant difference between the experts as compared with between auto and experts for both accuracy $F^2_{170} = 1.471$, $P = 0.233$ and kappa $F^2_{170} = 1.626$, $P = 0.200$.

For derived sleep measures, except for N2%, all other measures showed good to excellent ICC between the average of the two raters and auto (Table 4). In fact, except for latency, the agreement between auto and mean of the two raters was higher than that of agreement between the two raters. Between the two experts, agreement remained good to excellent for most measures, except for N1 time (ICC 0.594) and N2% (ICC 0.607). The overall agreement along with the 95% CI is presented in Table 4A.

For the primary respiratory outcomes including AHI and ODI, the agreement was excellent between raters as well as between raters and auto. For AHI, the ICC between the average of the two raters and auto was 0.958, indicating a near-perfect agreement. The agreement between the experts was lower at ICC 0.902, but was still close to excellent. A similar trend was also observed for ODI (Table 5).

With regard to the individual respiratory events, the agreement for apneas was good across the board. ICC between the experts was 0.880, while ICC between the average of the two experts and auto was 0.813. When individual apneas were subcategorized, the agreement

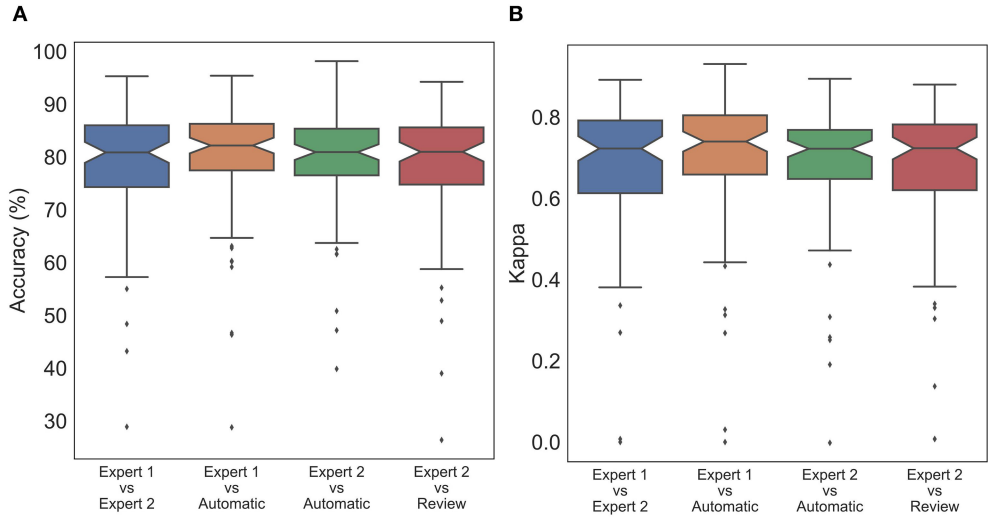

FIGURE 3
Box plot of subject wise **(A)** accuracy and **(B)** Cohen's Kappa comparing staging between experts and automatic scoring. No statistically significant difference was found between expert scores and automatic scores for both accuracy and Cohen's kappa.

TABLE 3 Table comparing accuracy and Cohen's kappa between subject wise measures and combined sleep stages.

	Accuracy		Kappa	
	Average	Combined	Average	Combined
Expert 1 vs. expert 2	78.08% ± 11.70%	78.29%	0.673 ± 0.172	0.702
Expert 1 vs. automatic	79.38% ± 11.08%	79.59%	0.695 ± 0.172	0.726
Expert 2 vs. automatic	79.52% ± 9.82%	79.59%	0.680 ± 0.158	0.713
Expert 1 vs. review	81.91% ± 13.34%	82.20%	0.740 ± 0.187	0.726
Expert 2 vs. review	78.20% ± 11.66%	78.41%	0.671 ± 0.179	0.703

Mean and standard deviations are shown for subject wise measures.

dropped substantially. Between the experts as well as between auto and average of the two experts, agreement was good for obstructive apnea, moderate for mixed apnea, and poor for central apnea. For hypopneas, agreement between auto and average of the two experts was poor, although the agreement between experts was good. A similar result was also observed for arousals. For desaturation events, the agreement remains excellent for all raters and between auto and raters. The results are summarized in Table 6A.

For AHI, which is the primary diagnostic criteria for sleep apnea, a scatter plot was obtained between experts and auto as well as between the mean of the two experts and auto (Figure 4). Pearson's correlation between the average of the two experts and auto was 0.972, indicating a near-perfect correlation. The correlation between the experts was also high at 0.929.

3.1. Manual review of automatic scores

The auto scores were thoroughly reviewed by expert 1. Following the review, the scores were compared with both experts. Since the review was done by expert 1, it is expected that the agreement of the reviewed scores would match better with that of expert 1. The agreement between expert 1 and automatic increased from 79.59 to 82.2% after the review (Figures 1B, C). Interestingly, Cohen's kappa remained completely unaffected by the review. Agreement with expert 2 dropped after the review from 79.59 to 78.41% (Figures 1D, E). The kappa also reduced from 0.713 to 0.703 following the review. To evaluate which epochs were affected following the review, the confusion matrix between the original auto scores and review was plotted (Figure 2A). A total of 10,160 epochs (11.6% of all epochs) were changed after the review. The three major changes were 1,901 epochs changed from N2 to N1, 1,634 epochs changed from Wake to N1, and 1,233 epochs changed from N2 to N3.

The agreement between the concordance of the two experts and automatic was excellent at 89.38%, with a kappa of 0.850 (Figure 2B). This only increased marginally after the review (89.81%, kappa 0.857) (Figure 2C). With regard to derived sleep measures, ICC for REM latency improved from 0.911 to 0.967 for latency and 0.863 to 0.963 for REM latency (Table 4B).

With regard to primary respiratory outcomes, ICC improved from 0.958 to 0.962 for AHI but declined for ODI from 0.986 to 0.934 following the review (Table 5B). For the individual respiratory events, we saw an improvement in ICC across the board, except for desaturation (Table 6B).

To mitigate any impact of memorization on the review process, the review process was separated from the scoring process by at least 6 months. Furthermore, the scoring and review were randomly

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TABLE 4 Intraclass correlation coefficient (ICC) (A) of various derived sleep measures compared against each pair of scorers, (B) between experts and average of the experts and automatic scores after review.

A.				
Measurement	Expert 1 vs. expert 2	Average vs. automatic	Expert 1 vs. automatic	Expert 2 vs. automatic
TST	0.873 (0.810 ± 0.920)	**0.945 (0.920 ± 0.960)**	0.904 (0.860 ± 0.940)	0.927 (0.890 ± 0.950)
Efficiency	0.844 (0.770 ± 0.900)	**0.935 (0.900 ± 0.960)**	0.879 (0.820 ± 0.920)	0.920 (0.880 ± 0.950)
N1 time	0.594 (0.440 ± 0.710)	**0.827 (0.750 ± 0.880)**	0.687 (0.560 ± 0.780)	0.796(0.700 ± 0.860)
N2 time	0.806 (0.720 ± 0.870)	**0.829 (0.750 ± 0.880)**	0.764 (0.660 ± 0.840)	0.806 (0.720 ± 0.870)
N3 time	0.756 (0.650 ± 0.830)	**0.857 (0.790 ± 0.900)**	0.855 (0.790 ± 0.900)	0.766 (0.660 ± 0.840)
REM time	0.793 (0.700 ± 0.860)	**0.873 (0.810 ± 0.920)**	0.775 (0.670 ± 0.850)	0.883 (0.830 ± 0.920)
N1%	0.753 (0.640 ± 0.830)	**0.896 (0.840 ± 0.930)**	0.807 (0.720 ± 0.870)	0.872 (0.810 ± 0.910)
N2%	0.607 (0.450 ± 0.730)	**0.713 (0.590 ± 0.800)**	0.539 (0.370 ± 0.670)	0.732(0.620 ± 0.820)
N3%	0.763 (0.660 ± 0.840)	**0.837 (0.760 ± 0.890)**	0.837 (0.760 ± 0.890)	0.746 (0.640 ± 0.830)
REM%	0.782 (0.680 ± 0.850)	**0.829 (0.750 ± 0.890)**	0.700 (0.570 ± 0.790)	0.869 (0.810 ± 0.910)
Latency	**0.972 (0.960 ± 0.980)**	0.911 (0.870 ± 0.940)	0.920 (0.880 ± 0.950)	0.889 (0.830 ± 0.930)
REM latency	**0.963 (0.940 ± 0.980)**	0.863 (0.800 ± 0.910)	0.867 (0.800 ± 0.910)	0.843 (0.770 ± 0.900)

B.		
Measurement	Expert 1 vs. expert 2	Average vs. review
TST	0.873 (0.810 ± 0.920)	**0.951 (0.930 ± 0.970)**
Efficiency	0.844 (0.770 ± 0.900)	**0.940 (0.910 ± 0.960)**
N1 time	0.594 (0.440 ± 0.710)	**0.831 (0.750 ± 0.890)**
N2 time	0.806 (0.720 ± 0.870)	**0.853 (0.780 ± 0.900)**
N3 time	0.756 (0.650 ± 0.830)	**0.826 (0.740 ± 0.880)**
REM time	0.793 (0.700 ± 0.860)	**0.902 (0.850 ± 0.930)**
N1%	0.753 (0.640 ± 0.830)	**0.886 (0.830 ± 0.920)**
N2%	0.607 (0.450 ± 0.730)	**0.703 (0.580 ± 0.800)**
N3%	0.763 (0.660 ± 0.840)	**0.815 (0.730 ± 0.880)**
REM%	0.782 (0.680 ± 0.850)	**0.878 (0.820 ± 0.920)**
Latency	**0.972 (0.960 ± 0.980)**	0.967 (0.950 ± 0.980)
REM latency	0.963 (0.940 ± 0.980)	0.963 (0.940 ± 0.980)

Numbers in brackets indicate 95% confidence interval. When comparing ICC between **(A)** experts and automatic vs. average and **(B)** the experts and automatic against the average after review, bold figures indicate better performance.

assigned to a given technologist based on operational constraints. This further reduces the chances that the same technician scores and reviews the same record.

3.2. Time motion study and productivity gains

Manual scoring by **expert 1** took an average of 4,243 s (70.7 min). Automatic scoring took an average of 42.7 s per record. The time taken for autoscoring coupled with a thorough review of the scores by **expert 1** took an average of 1,929 s (32.1 min), representing average time savings of 2,314 s (38.6 min) per patient PSG report generated ($p < 0.001$). With an estimated saving of 38.6 min per patient PSG report, total savings amounts to 28,950 min per year (482.5 h) or a total of 0.25 FTE savings per year based on an estimated load of 750 patients per year requiring sleep disorder-related investigations at an acute care institution in Singapore and FTE of one nurse being equivalent to 1,940.4 h per annum. This is equivalent to 0.33 FTE per 1,000 patients-year.

4. Discussion

The AASM in a recent position statement stated that PSG is well-suited for analysis using AI and has the potential to improve sleep laboratory efficiency and yield greater clinical insights (16). The position statement comes in light of recent advances in machine learning (ML) algorithms, specifically DL-based algorithms that have demonstrated phenomenal performance improvements across the spectrum of applications (17). DL algorithms train models directly from data without relying on hand-engineered features or rules (18).

TABLE 5 Intraclass correlation coefficient (ICC) of (A) important respiratory indices compared against each pair of scorers, (B) automatic scores before and after review as compared with average of the two experts.

A.				
	Expert 1 vs. expert 2	Average vs. automatic	Expert 1 vs. automatic	Expert 2 vs. automatic
AHI	0.902 (0.850 ± 0.930)	**0.958 (0.940 ± 0.970)**	0.972 (0.960 ± 0.980)	0.891 (0.840 ± 0.930)
ODI	0.870 (0.810 ± 0.910)	**0.986 (0.980 ± 0.990)**	0.957 (0.930 ± 0.970)	0.948 (0.920 ± 0.970)
B.				
		Average vs. automatic	Average vs. review	
AHI		0.958 (0.940 ± 0.970)	**0.962 (0.940 ± 0.980)**	
ODI		**0.986 (0.980 ± 0.990)**	0.934 (0.900 ± 0.960)	

Numbers in brackets indicate 95% confidence interval. When comparing ICC between (A) experts and automatic vs. average, and (B) automatic against the average, before and after review, bold figures indicate better performance.

TABLE 6 Intraclass correlation coefficient (ICC) of (A) various respiratory counts compared against each pair of scorers, (B) automatic scores before and after review as compared with average of the two experts.

A.				
	Expert 1 vs. expert 2	Average vs. automatic	Expert 1 vs. automatic	Expert 2 vs. automatic
Apneas	**0.880 (0.820 ± 0.920)**	0.813 (0.730 ± 0.870)	0.743 (0.630 ± 0.820)	0.767 (0.660 ± 0.840)
Central apneas	**0.453 (0.270 ± 0.610)**	0.390 (0.200 ± 0.560)	0.522 (0.350 ± 0.660)	0.496 (0.320 ± 0.640)
Obstructive apneas	**0.780 (0.680 ± 0.850)**	0.753 (0.640 ± 0.830)	0.689 (0.560 ± 0.790)	0.720 (0.600 ±0.810)
Mixed apneas	**0.812 (0.730 ± 0.870)**	0.637 (0.490 ± 0.750)	0.663 (0.530 ± 0.770)	0.658 (0.520 ± 0.760)
Hypopneas	**0.846 (0.770 ± 0.900)**	0.307 (0.100 ± 0.490)	0.332 (0.130 ± 0.510)	0.665 (0.530 ±0.770)
Arousals	**0.778 (0.680 ± 0.850)**	0.458 (0.270 ± 0.610)	0.314 (0.110 ± 0.490)	0.742 (0.630 ± 0.820)
Desaturations	0.987 (0.980 ± 0.990)	**0.996 (0.990 ± 1.000)**	0.993 (0.990 ±1.000)	0.970 (0.950 ± 0.980)
B.				
		Average vs. automatic	Average vs. review	
Apneas		0.813 (0.730 ±0.870)	**0.833 (0.750 ± 0.890)**	
Central apneas		0.390 (0.200 ± 0.560)	**0.655 (0.520 ± 0.760)**	
Obstructive apneas		0.753 (0.640 ±0.830)	**0.823 (0.740 ± 0.880)**	
Mixed apneas		0.637 (0.490 ± 0.750)	**0.667 (0.530 ± 0.770)**	
Hypopneas		0.307 (0.100 ± 0.490)	**0.622 (0.470 ± 0.740)**	
Arousals		0.458 (0.270 ±0.610)	**0.889 (0.830 ± 0.930)**	
Desaturations		**0.996 (0.990 ± 1.000)**	0.976 (0.960 ± 0.980)	

Numbers in brackets indicate 95% confidence interval. When comparing ICC between (A) experts and automatic vs. average and (B) automatic against the average, before and after review, bold figures indicate better performance.

As per the AASM, the goal of AI should be to augment expert evaluation of sleep data. While accuracy and reliability are important considerations for such an AI, there are other considerations that are equally important, including logistical, security, ethical, and legal. Commercial systems must address all these considerations before they are allowed to be marketed by the regulators. It is not surprising that despite the strong interest in AI-based sleep scoring within the academic field (19, 20), only a handful of commercial AI scoring solution exists in the market that fully exploits these recent advances in AI. It is, therefore, important to benchmark the performance of such commercial systems as they potentially have a huge impact on clinical practice.

In the present study, we benchmarked the performance of an automatic sleep scoring system called Neurobit PSG on patients referred to a sleep lab with a suspected sleep disorder. The software is trained on large and highly diverse PSG datasets with a good mix of healthy and patient population. To establish a baseline for the scoring, we scored the records independently by two different sets of scorers. Expert 1 was a set of expert sleep technologists at the sleep lab, while expert 2 was a single RPSGT at a commercial scoring company. To avoid any systematic bias in the training of the experts, we ensured that the two sets of experts were geographically isolated. We demonstrated a high degree of concordance between the automatic system and expert scorers. With regard to sleep staging, at an epoch-by-epoch level, the agreement between automatic and experts was consistently higher than the agreement between the two experts. However, no statistically significant difference was observed between expert and manual scoring. With regard to key derived

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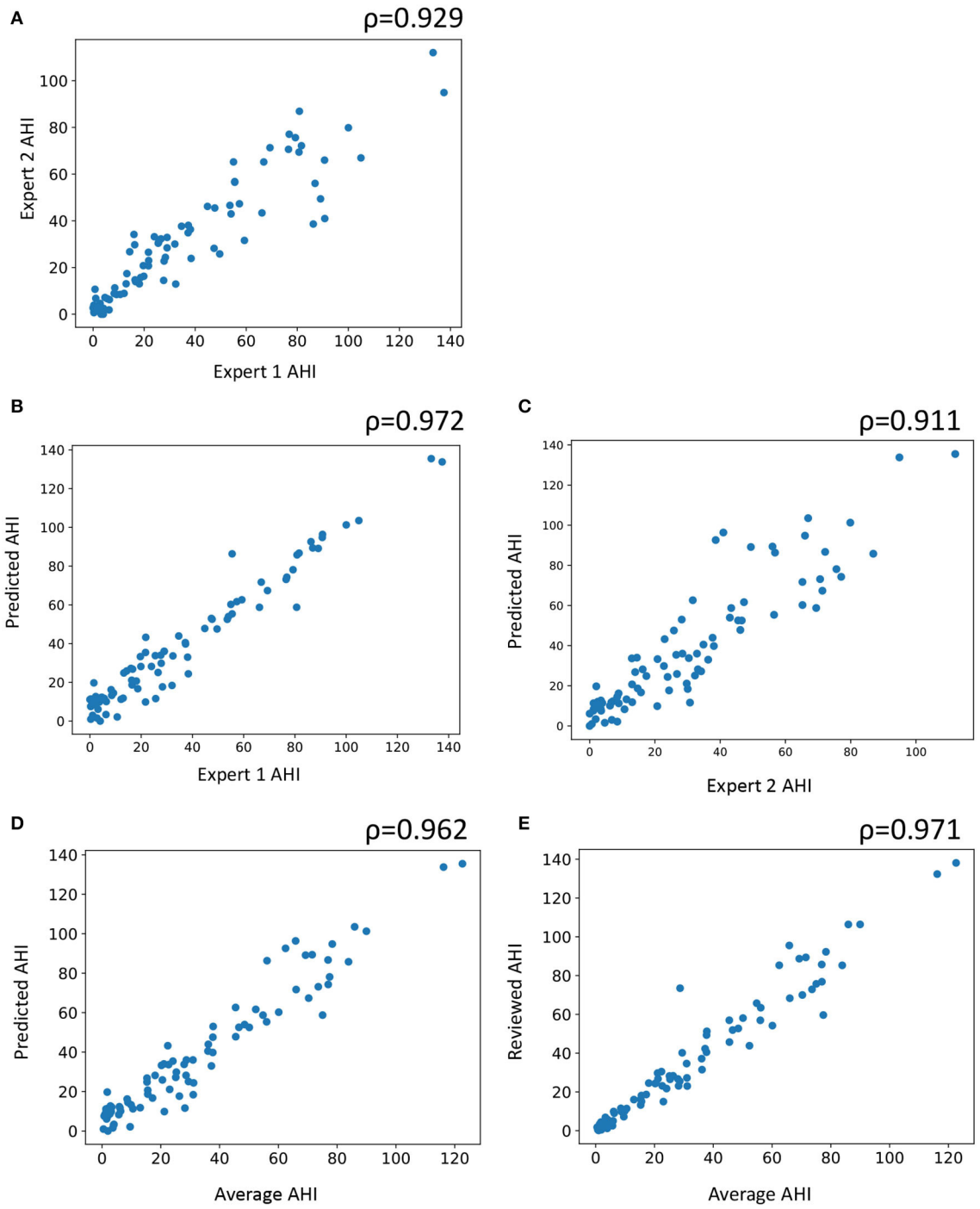

FIGURE 4
Scatter plot of subject wise apnea-hypopnea index (AHI) estimated between **(A)** the two experts, **(B)** automatic and expert 1, **(C)** automatic staging and expert 2, **(D)** automatic staging and average of both experts, and **(E)** automatic staging after review and average of the two experts. AHI is computed by counting the number of apneas and hypopneas and dividing it by the total sleep time. ρ indicates Pearson's correlation.

sleep measurements, including TST, sleep efficiency, time spent in various sleep stages, WASO, and latency, the agreement between auto and the experts was excellent. For most measures, there was a higher agreement between auto and the experts than between the two experts. There was excellent agreement between auto and the experts for primary respiratory indices, including AHI and ODI. However, agreement for individual respiratory events can improve.

A thorough review of the scores (including sleep stages and respiratory events) was carried out by expert 1. It was observed that a thorough review of staging introduced bias into the scores and had a negligible or negative impact on agreement. A similar trend was observed for oxygen desaturation events. For the primary respiratory outcome, agreement for AHI improved while that for ODI reduced. For individual respiratory events,

we observed significant improvement in agreement following the review. Based on these observations, an optimal review strategy is proposed.

In the following sections, we discuss these results in greater detail.

4.1. Sleep staging performance

The overall agreement between the two experts was 78.29%, with $\kappa = 0.702$ when epochs across all subjects were combined. This is in line with the previously reported IRR for subjects with suspected sleep disorders. In a study comparing IRR between experienced scorers from eight European sleep laboratories within a large sample of patients with various sleep disorders (7), the overall level of agreement was found to be 76.8%, with $\kappa = 0.682$. The authors observed that the IRR varied significantly across different disease conditions. For individual sleep stages, the highest agreement was for REM, followed by wake, N3, N2, and N1. The study relied on an outdated standard for sleep scoring rules published by Rechtschaffen and Kales (21). The R&K standard has significant limitations (22) and has been superseded by the modern AASM standards. A more recent study (9) was carried out involving experts from nine center members of the Sleep Apnea Genetics International Consortium (SAGIC) to establish IRR across international sleep centers. The scoring was done on 15 previously recorded PSGs as per the AASM guidelines. The overall agreement across all epochs was found to be $\kappa = 0.63$ (95% CI 0.62–0.63), indicating substantial agreement. Agreement for REM and wake was similar ($\kappa = 0.78$), followed by N3 ($\kappa = 0.67$), N2 ($\kappa = 0.6$), and finally N1 ($\kappa = 0.31$). In another study, inter-lab reliability between US and Chinese sleep centers was accessed. Five doctors from China and two doctors from the USA scored 40 overnight PSG records as per the AASM standard. The overall agreement was observed at $\kappa = 0.75$. Agreement was highest for REM and wake and lowest for N1. To quantify and improve IRR, the AASM started an inter-scorer reliability program (11). A small dataset comprising 9 record fragments (1,800 epochs) was scored by more than 2,500 scorers, most with 3 or more years of experience. The overall agreement across all epochs and scorers was 82.6%. Again, agreement was highest for REM (90.5%), followed very closely by N2 and wake (85.2 and 84.1%, respectively). Agreement was lower for N3 (67.4%) and lowest for N1 (63%). Unfortunately, Cohen's kappa statistic was not provided in the study.

The IRR between the independent experts provided us with a benchmark to compare against for automatic staging. We observed that the staging performance of the automatic system was similar to that of experts and consistent with prior findings. A stage-wise comparison was also consistent with prior observations, with the highest agreement being for wake, followed by REM, N2, N3, and N1. Both subject level and combined agreement were higher between auto and the expert as compared with between the experts. This was also reflected in the derived measures like TST, WASO, and time spent in individual stages. This is not surprising as most of the derived measures are directly linked to epoch-by-epoch accuracy. The only derived measure where experts had a better agreement compared with between expert and auto was latency. This is interesting as a single incorrectly identified sleep epoch can widely affect latency measurement, even if, at a statistical level, epoch-by-epoch staging accuracy of an automatic system might be indistinguishable from experts. ICC for auto vs. experts was good to excellent (ICC 0.945 for TST and ICC 0.863 for REM latency), there is value in the expert spending some time cross-checking the first sleep and REM stages detected by the autoscoring system. The AASM inter-scorer reliability program also observed that one of the epochs of highest disagreement was REM after N2 (10). We discuss data-driven recommendations for expert review in a later section.

4.2. Scoring of respiratory events

The IRR for detecting respiratory events is not as extensively studied as IRR for sleep staging. For respiratory events, the exact location and duration of the events are of less value. Instead, clinical outcomes are associated with the count of such events, sometimes normalized by the TST in the form of indices. Therefore, IRR for respiratory events is evaluated by comparing the event counts/indices across scorers. The AHI and ODI are two such primary outcome measures of sleep-disordered breathing. ICC is usually the metric used to quantify reliability.

IRR for respiratory events is strongly dependent on the rules and specifications. For instance, IRR across three sleep technologists at one centralized scoring center was excellent when the respiratory events were associated with a desaturation event, rather than the presence of an associated EEG arousal (23). This is not surprising as IRR for EEG arousals is usually low to moderate (9, 24, 25). Despite this, the AASM introduced a major change in the definition of hypopnea in 2012. Compared to the 2007 standard (6) where hypopneas were associated with a $\geq$ 4% drop in oxygen desaturation, the 2012 standard (3) required the presence of $\geq$ 3% drop in oxygen desaturation and/or an associated EEG arousal. It was observed that the 2012 standard almost always resulted in a higher number of hypopnea events (26). Despite a potential reduction in IRR, the 2012 definition is clinically more relevant (27). Therefore, in the present analysis, we scored the studies based on the updated 2012 definition of hypopnea.

Prior work has shown IRR to be excellent for primary respiratory outcomes, even though agreement can vary widely for individual respiratory events. Within the SAGIC study, Magalang et al. tried to assess the respiratory IRR in addition to staging agreements among the international sleep centers. For AHI, they observed an ICC of 0.95 (95% CI: 0.91–0.98) and for ODI, ICC was 0.97 (95% CI 0.93–0.99), indicating excellent agreement across raters. For individual events, the ICC was lower. ICC was 0.73 (95% CI 0.55–0.88) for total apneas and 0.80 (95% CI 0.65–0.91) for total hypopneas. Subcategorizing apneas further reduced the agreements: 0.70 for obstructive, 0.46 for central, and 0.42 for mixed. In another study, 28 determined the inter-site agreement in respiratory events. They scored a set of 70 records by 10 technologists from five different sleep centers, using three different hypopnea criteria described in the 2007 AASM standards. For AHI, the across-site ICC was excellent at 0.984 (95% CI 0.977–0.990). Across-site ICC for obstructive apnea was 0.861 (95% CI 0.837–0.881) and for central apnea was 0.683 (95% CI 0.640–0.722). For hypopneas, as per the 2007 recommended definitions, the inter-site ICC was 0.843 (95% CI 0.820–0.870). It must be noted that both studies used the conservative definition of hypopnea and oxygen desaturation in the 2007 recommendations. In addition, the second

study marked mixed apneas as obstructive (28). Therefore, their results might be inflated compared with scoring using the 2012 rules.

The AASM inter-scorer reliability program also explored respiratory events (11). The sample included 15 monthly records with 200 epochs each. These were scored by over 3,500 scorers. Instead of identifying the location and count of the events, the scorers had to identify if a particular event happened in a shown epoch. Therefore, although the outcome gave an indication of agreement, it is not directly translatable to the actual detection of respiratory events which relies on the count of such events. Nonetheless, within this framework, the correct event type was designated as the majority score and the percentage agreement was used as a proxy for IRR. Overall, 3,000 epochs were included in the analysis, of which 364 (12%) were scored to have a respiratory event by the majority. Out of 364, 172 were hypopnea, 150 were obstructive apnea, 41 were central apnea, and only 1 was mixed apnea. For hypopnea, agreement was 65.4%, obstructive apnea was 77.1%, central was 52.4%, and mixed apnea was 39.8%. The overall agreement for detecting any respiratory event was 88.4%. In other words, while the overall agreement was very good, disagreements in scoring apnea vs. hypopnea and type of apnea were common.

In this study, we observed excellent agreement between automatic and expert scores for both AHI and ODI (ICC 0.958 and 0.986, respectively). In both the key measures, agreement between auto and the experts was higher than agreement between the two experts. Pearson's correlation between average of the two experts and auto was near-perfect, with $\rho = 0.962$. The IRR dropped for individual respiratory events both between the experts and between expert and auto. For all apneas, obstructive apneas, and oxygen desaturation events, the agreement between auto and the experts was close to between the experts. For central apneas, mixed apneas, hypopneas, and arousal, auto appeared to perform much worse than expert scorers. Even though the overall performance of auto for primary measures was excellent, the performance on these specific respiratory events can be improved further. Expert review of these events might play a significant role in improving these aspects.

4.3. Augmenting the sleep technologist

The primary goal of AI-based automatic scoring system is to empower sleep technologists by augmenting their capabilities. To achieve the highest levels of accuracy, reliability, and consistency, the experts must work in concert with AI. To fulfill this, it is important to understand the limitations of both manual and automatic scoring. Therefore, we carried out a thorough review of the scores by the experts at the clinic (expert 1). We did not optimize the review at this stage as the limitations of the auto scores were not known *a priori* and doing so would introduce bias into the process. Once the limitations were well understood, we proposed a data-driven approach to review the scores optimally.

Another reason why expert supervision is important is because AI-based systems can fail in ways that are counter-intuitive to humans. Under specific edge cases, AI can make mistakes that an expert would never make. For instance, on one occasion (outside the scope of the current study), due to an incorrect export of the PSG record, the data were incorrectly encoded in microvolts when in reality it was in volts. An error like this would be easily caught by the expert, although the AI failed to recognize it. Although the system was updated to handle such errors in the future, it is impossible to account for other such unforeseen edge cases.

4.4. Impact of a thorough review on staging

We already demonstrated that epoch-by-epoch staging was indistinguishable from experts. The only area where there is a scope to improve is latency. Following the thorough review, we observed that the majority of changes made by the experts was from N2 to N1, Wake to N1, and N2 to N3. These three changes accounted for nearly half of all the changes. This is in line with prior findings (10), where most of the confusion occurs between Wake, N2, and N1. The authors found that disagreement with stage N3 is almost entirely based on confusion with N2. Interestingly after review, the agreement with expert 1 did not change in terms of kappa, although there was an increase in accuracy from 79.59 to 82.2%. The agreement with expert 2 actually dropped from 79.59 to 78.41%. For the concordant epochs where both experts agree, it appears that the review had minimal to no effect (Figures 2B, C). Most epochs affected by the review probably did not have a clear classification. In a study analyzing inter-scorer variability (12), the authors observed that most of the variability is largely due to epochs that are difficult to classify and may not have a clear classification. This would explain why agreement following the review did not improve. As the automatic scores were already indistinguishable from the experts, the thorough review simply introduced a bias toward expert 1 while reducing agreement with expert 2.

While looking at derived sleep measures, agreement of automatic with expert was already better than between the experts for most measures, except for latency. Following review, we observed an increase in agreement for the latency measures. Therefore, we recommend a quick scan of the automatic scores with a focus on the first sleep and REM stages following wake as a strategy to optimally review sleep stages.

4.5. Impact of a thorough review on respiratory events

For respiratory events, automatic measurement of primary outcomes shows excellent agreement with experts, but there is significant scope for improvement for individual respiratory events. This is evident from the significant improvement in agreement for most respiratory events following the review. The only event that was negatively affected by the review was desaturation. ICC agreement for oxygen desaturation events is already almost perfect for automatic scoring. Therefore, our recommendation is to do a thorough review of respiratory events with a specific focus on arousals and apnea subtypes, while ignoring desaturation events.

Despite an additional review of sleep scoring manually by **expert 1** after completion of a first round of autoscoring, the average scoring time was reduced from 71 to 32 min. With the proposed optimal review strategy, we expect the scoring time to further reduce to ∼15 min. We expect the automatic scoring system to have a significant impact on the economics and throughput of a sleep lab. A detailed analysis will be conducted and will be reported elsewhere.

4.6. Time motion study findings and impact on productivity

To the best of our knowledge, this is the first study to report potential productivity gains with the use of an automated software assessing PSG reports from patients with suspected sleep disorders. As highlighted earlier, with an estimated saving of 38.6 min per patient PSG report, this amounts to a total of 0.25 FTE savings per year based on an estimated load of 750 patients per year, assuming no improvements to the software over time and a stagnant patient workload. A further increase in productivity gains could be realized through improvements in software capability and accuracy, which would allow the sleep technologists to make fewer amendments during their manual checks on the automated PSG scorings, as well as a potential increase in patient workload due to the increase in suspected sleep disorders in the population. In the absence of any manual review, automatic scoring took only 42.7 s on average compared to 4,243 s for manual scoring, representing a 99.0% reduction in scoring time. With the rapid advancement in ML and increasing trust in AI systems, scoring might become an instantaneous or even a real-time process in the future.

5. Comparison with other commercial autoscoring systems

Most PSG data acquisition software includes some form of autoscoring system. Unfortunately, the performance of these systems has been less than satisfactory. These systems are mostly used to automatically identify oxygen desaturation events and leg movements. Most existing sleep-scoring solutions are based on rules or hand-engineered features and do not exploit recent advances in DL. DL-based algorithms in general perform better than rules or feature-based methods and generalize well beyond the training dataset. This is especially true when sufficiently large training datasets are available. To the best of our knowledge, EnsoSleep (Ensodata, WI, USA) is the only commercial solution cleared by the FDA that utilizes modern AI technologies. The most recent scoring performance of EnsoSleep is published in an abstract (29). The validation was carried out on 100 adult patients. The PSG records were scored by three RPSGTs and a 2/3 consensus was used as the ground truth. The automatic scoring showed very good agreement with the consensus scores. For respiratory events, a 30-s epoch was marked to contain an event if 2/3 of the experts agreed on the presence of it within the epoch. This was an unusual way of comparing respiratory scoring performance. Nonetheless, they demonstrated good performance for standard AHI thresholds. Commercial solutions that are well validated include Philips Somnolyzer (Philips Respironics, PA, USA), Morpheus 1 (WideMed, IL, USA), and Michele (Cerebra Health Inc., Winnipeg, Manitoba, Canada).

The most up-to-date validation (30) of the Philips Somnolyzer system was carried out on 97 records and scored by certified technologists from four sleep laboratories. The average correlation between expert-reviewed Somnolyzer scored AHI and experts was 0.930. For the hypopnea index, the pair-wise correlation varied between 0.570 and 0.940; for the central apnea index, the pair-wise correlation varied between 0.800 and 0.920; and for the obstructive apnea index, the pair-wise correlation varied between 0.790 and 0.880. For sleep staging, pair-wise ICC between expert reviewed Somnolyzer and the four experts varied between 0.30 and 0.60 for N1, 0.03 and 0.26 for N2, 0.10 and 0.24 for N3, 0.89 and 0.94 for REM, and 0.17 and 0.82 for the arousal index. Except for REM, differences were observed between automated and experts for the percentage of sleep in N1, N2, N3, and arousal index. Most metrics provided in the study were already reviewed by experts, and the scoring was carried out using more conservative 2007 AASM standards, which might also inflate agreement.

Validation for Michele's scoring system was carried out on 70 records (24) and scored by ten experts from five different sleep labs. The ICC agreement was 0.96 for AHI, 0.63 for central apnea, and 0.94 for obstructive apnea. For arousals, ICC was 0.39 for REM arousals and 0.83 for NREM arousals. ICC agreement for TST was 0.87, time in N1 was 0.56, time in N2 was 0.84, time in N3 was 0.47, time in REM was 0.64, sleep efficiency was 0.74, and REM latency was 0.55. An epoch-by-epoch agreement was not presented. An important limitation of the study was that a majority of the participants were healthy. The authors counted mixed apnea as obstructive. In addition, the records were scored as per the 2007 AASM standards, which could again inflate the agreement.

Morpheus 1 is the oldest of the three systems. The validation was carried out on 31 diagnostic PSG records and scored by two experts (25). Agreement between the two experts and Morpheus 1 was 77.7% with $\kappa = 0.67$ and 73.3% with $\kappa = 0.61$, while agreement between the two experts was 82.1% with $\kappa = 0.73$. The ICC for Morpheus 1 and expert 1 and expert 2 was 0.72 and 0.58, respectively, for the arousal index and 0.95 for both the experts for the respiratory disturbance index. The performance of Morpheus 1 was not on par with the experts.

Notwithstanding the fact that a direct comparison between Neurobit PSG with these systems is not possible given the datasets and the raters were different, Neurobit PSG consistently performed better across all measures for sleep staging despite scoring according to the more stringent 2012 AASM rules. Notably, for most key sleep and respiratory measurements, the agreement between auto and the experts was higher than that between the two experts.

6. Strengths and limitations

Some of the key strengths of the study are the relatively large and representative dataset, which was scored by trained sleep technologists independently. The two experts were from completely different continents to remove any potential training bias. The scoring was conducted in compliance with the latest AASM guidelines, which are more demanding as compared with previous standards. We provided an epoch-by-epoch comparison for staging including accuracy and kappa measures at both an aggregate and subject level. For respiratory events, we used a two-way random-effects model based on a single rater for absolute agreement to ensure the generalizability of our results beyond the raters involved in the study. The dataset used for benchmarking was completely independent of any training or testing data used in the development of the AI algorithm. This is important, as training, testing, and validating AI algorithms on the same dataset can introduce bias and significantly inflate the results. The study also provides productivity gain estimates through a thorough assessment using a time motion study. Despite all the strengths, the study has some limitations.

There are only two sets of raters to estimate the baseline agreements. A larger number of raters could help make better IRR estimates for events that are less frequent, like mixed and central apnea and measures where agreements are known to be low between the experts like arousals and N1 duration. Another limitation of the study is that the scoring solution cannot be directly compared with existing commercial solutions. The AASM is currently working on a new platform to evaluate the performance of AI scoring packages. This is an excellent way to transparently evaluate commercial software solutions.

7. Conclusion

We benchmarked the performance of a new commercial sleep-scoring solution on a representative sample of patients with suspected sleep disorders. We demonstrated performance indistinguishable from experts in terms of staging and primary respiratory outcomes. Based on the review of the automatic scores by the experts, we observed the marginal utility of a thorough review of the staging. Although an extensive review of arousals, hypopnea, and apnea subtypes will improve scoring performance. We expect a significant benefit of AI-augmented sleep scoring in improving lab efficiency and scoring standardization, as well as potentially improving work productivity for sleep technologists in the healthcare setting.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Singhealth Centralised Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

The study was designed by HW, YM, BC, HO, YP, AP, and KK. AP, SBi, AA, and BC contributed to the analysis of data. YP was responsible for overseeing data collection and scoring at the hospital. YP, BC, AP, and KK were responsible for data handling and security. BC, AP, YM, HW, and SBh contributed to the write-up of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AP and KK are shareholders in Neurobit, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The association between sleep duration, respiratory symptoms, asthma, and COPD in adults

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Introduction: The association between sleep duration and cough, wheezing, and dyspnea was unclear. This research aimed to test this relationship.

Methods: Research data were obtained from people who participated in the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2012. We used weighted logistic regression analysis and fitted curves to explore the association between sleep and respiratory symptoms. In addition, we investigated the association between sleep duration, chronic obstructive pulmonary disease (COPD), and asthma. The stratified analysis is used to analyze inflection points and specific populations.

Results: The 14,742 subjects are weighted to reflect the 45,678,491 population across the United States. Weighted logistic regression and fitted curves show a U-shaped relationship between sleep duration and cough and dyspnea. This U-shaped relationship remained in people without COPD and asthma. The stratified analysis confirmed that sleep duration before 7.5 h was negatively associated with cough (HR 0.80, 95% CI 0.73–0.87) and dyspnea (HR 0.82, 95% CI 0.77–0.88). In contrast, it was positively associated with cough and (HR 1.30, 95% CI 1.14–1.48) dyspnea (HR 1.12, 95% CI 1.00–1.26) when sleep duration was >7.5 h. In addition, short sleep duration is associated with wheezing, asthma, and COPD.

Conclusion: Both long and short sleep duration are associated with cough and dyspnea. And short sleep duration is also an independent risk factor for wheezing, asthma, and COPD. This finding provides new insights into the management of respiratory symptoms and diseases.

KEYWORDS

sleep duration, cough, wheezing, dyspnea, chronic obstructive pulmonary disease, asthma

Introduction

Coughing, wheezing, and dyspnea are common respiratory symptoms in adults. Two studies show that more than 50% of adults have at least one respiratory symptom (1, 2). Frequent respiratory symptoms bring attention to how these symptoms affect health. The research found that respiratory symptoms were associated with impaired quality of life even in the general population without chronic obstructive pulmonary disease (COPD) and asthma (3). In addition, in the general population, the presence of respiratory symptoms can increase the risk of all-cause mortality (4, 5).

Proper sleep duration is necessary for good health, and the American Sleep Foundation supports a daily sleep duration of 7–8 h for adults (6). However, since 1985, the proportion of adults with ≤6 h of sleep has gradually increased (7). Short sleep duration is considered a public health epidemic, associated with cardiovascular disease, obesity, and cancer (8). Moreover, long sleep duration is a growing concern and is a risk contributor to mortality and morbidity (9, 10).

Both long and short sleep duration seems to be factors affecting health, while the association between sleep duration and cough, wheezing, and dyspnea was unclear. Therefore, we plan to conduct studies to analyze the relationship between different sleep durations and coughing, wheezing and dyspnea. We also plan to analyze the relationship between sleep time, asthma, and COPD. The study population is from the 2005 to 2012 National Health and Nutrition Examination Survey (NHANES).

Materials and methods

Study population

National Health and Nutrition Examination Survey is a study based on the entire US population. Data collection included home screening, interviews, and physical examination (11). Each year, the NHANES staff selects a sample of 15 counties (about 5,000 people) from across the United States and calculates the sampling weights. With complex sampling weights, the population sampled reflects the overall US population. All information from the NHANES project is available on the official NHANES website (12). These data are de-identified and open to the public and therefore do not require the consent of the medical ethics committee.

Data for the study were obtained from participants who participated in the Sleep Duration Questionnaire from 2005 to 2012. The participants who performed the respiratory symptoms questionnaire were ≥40 years, so we only covered this subset of subjects. **Supplementary Figure 1** illustrates the detailed inclusion and exclusion criteria.

Sleep duration

The sleep duration is the answer to the question: "How much sleep {do you/does SP} usually get at night on weekdays or workdays?". Sleep duration is classified as short sleep duration (<7 h), normal sleep duration (7–8 h), or long sleep duration (>8 h). In addition, we defined sleep disorders as an affirmative answer to the following question "Ever told doctor had trouble sleeping?".

Respiratory symptoms

Cough was classified as answering yes to the following questions. "Do you usually cough on most days for three consecutive months or more during the year?" to determine. Wheezing and dyspnea were defined as affirmative answers to the following questions. "In the past 12 months, have you had wheezing or whistling in your chest?" and "Have you had shortness of breath either when hurrying on the level or walking up a slight hill?".

Study covariates

We included demographic data to reduce potential bias, including gender, age, body mass index (BMI), race, smoking history, and education. Subjects receiving lung health questions were ≥40 years of age. The race is divided into White, Mexican American, Black, and Other races. Because of the small number of people with BMI <20, they were divided into three groups (<25, 25–30, and >30 kg/m^2). Smoking status was categorized as never (smoking less than 100 cigarettes in a lifetime), previous (Smokes more than 100 cigarettes but has quit), and current.

Diabetes was defined as the presence of one of the following conditions (diagnosed by an internist, glycosylated hemoglobin ≥ 6.5%, fasting glucose ≥ 7.0 mmol/L, taking glucose-lowering medication, glucose tolerance test ≥ 11.1 mmol/L) (13). Hypertension was defined as the presence of one of the following conditions (diagnosed by a physician, taking antihypertensive medication, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg) (14). The patient reports the presence of cardiovascular disease as the presence of any of the following (congestive heart failure, heart attack, coronary artery disease, stroke) (15). COPD is defined as a diagnosis of "chronic bronchitis or emphysema." The presence of asthma was defined by the participant's affirmative answer to the question, "Has a doctor or other health professional ever told you that you had asthma?" (16).

Statistical analysis

Categorical data conforming to a normal distribution are described as numbers (percentages), and continuous variables are means ± standard deviations. Skewed data are represented by the median (25th–75th percentile). Kruskal Wallis and Chi-square (or Fisher's exact) tests compare covariates.

Based on the sampling weights of the data, we used logistic regression and fitted curves to investigate the relationship between sleep duration and cough, wheeze, and dyspnea. We also investigated the relationship between sleep disorders and respiratory symptoms. Three models were adjusted to ensure the stability of the results. Furthermore, we also investigated the relationship between sleep duration, COPD, and asthma. Subgroup

and stratification analyses were used to explore curve relationships and population classification.

The missing data for BMI was 5.3%, and we applied multiple interpolations to adjust the data. We also analyzed the data's sensitivity before interpolating to reduce the error. The analysis was performed using R V4.1.3 and free statistical software (1.7).

Results

Baseline characteristics

A total of 14742 subjects were enrolled in our research (Supplementary Figure 1). After weighting, these participants reflect a population of 45,678,491 across the United States. Table 1 shows that 5,897 people had <7 h of sleep, 7,682 people had 7–8 h, and 1,163 people had >8 h of sleep. Comorbidities and respiratory symptoms were lower in the 7–8 h sleepers compared to the other two groups.

Association between sleep duration and respiratory symptoms

Table 2 shows the relationship between sleep duration (<7, 7–8, >8 h) and respiratory symptoms. Using 7–8 h as a reference, short and long sleep duration was associated with a 41 and 56% increase in cough, respectively. Less sleep is also associated with the occurrence of wheezing and dyspnea.

Figures 1A, C shows a U-shaped curve between sleep duration and cough and dyspnea. Based on this result, we performed a

TABLE 1 Characteristics of participants, 2005–2012 NHANES (*n* = 14,742).

Variables	Sleep duration (h)			*P*
	7–8 (*n* = 7,682)	<7 (*n* = 5,897)	>8 (*n* = 1,163)	
Age, mean ± SD	60.4 ± 12.7	58.6 ± 12.1	66.1 ± 13.2	<0.001
Female, *n* (%)	3896 (50.7)	2959 (50.2)	641 (55.1)	0.008
Race/ethnicity, *n* (%)				<0.001
Non-Hispanic White	4,054 (52.8)	2,346 (39.8)	668 (57.4)	
Mexican American	1,152 (15.0)	824 (14.0)	148 (12.7)	
Non-Hispanic Black	1,297 (16.9)	1,723 (29.2)	225 (19.3)	
Other race	1,179 (15.3)	1,004 (17.0)	122 (10.5)	
BMI*, *n* (%)				<0.001
<25	1,975 (27.2)	1,346 (24.0)	313 (29.5)	
25–30	2,684 (37.0)	1,941 (34.6)	338 (31.9)	
>30	2,604 (35.9)	2,317 (41.3)	409 (38.6)	
Smoke, *n* (%)				<0.001
Never smoker	3,983 (51.8)	2,879 (48.8)	557 (47.9)	
Former smoker	2,446 (31.8)	1,694 (28.7)	388 (33.4)	
Current smoker	1,253 (16.3)	1,324 (22.5)	218 (18.7)	
Education, *n* (%)				<0.001
< High school diploma	1,127 (14.7)	878 (14.9)	237 (20.4)	
Completed high school	2,880 (37.5)	2,403 (40.7)	471 (40.5)	
≥College	3,675 (47.8)	2,616 (44.4)	455 (39.1)	
Comorbidities, n (%)				
Asthma	805 (10.5)	901 (15.3)	141 (12.1)	<0.001
COPD	530 (6.9)	509 (8.6)	93 (8.0)	<0.001
CVD	1,132 (14.7)	1,030 (17.5)	307 (26.4)	<0.001
Diabetes	1,747 (22.7)	1,559 (26.4)	349 (30.0)	<0.001
Hypertension	4,082 (53.1)	3,400 (57.7)	737 (63.4)	<0.001
Respiratory symptoms, n (%)				
Cough	693 (9.0)	756 (12.8)	163 (14.0)	<0.001
Wheezing	933 (12.1)	1,027 (17.4)	160 (13.8)	<0.001
Dyspnea	2,240 (29.2)	2,263 (38.4)	440 (37.8)	<0.001

*Missing value: 815/14741, 5.53%. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

TABLE 2 Association of sleep duration (h) and respiratory symptoms.

	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*	Model 3 OR (95% CI)	*P*
Cough						
Sleep duration (h)						
7–8	1(Ref)		1(Ref)		1(Ref)	
<7	1.60 (1.36–1.88)	<0.001	1.50 (1.26–1.79)	<0.001	1.44 (1.20–1.73)	<0.001
>8	1.84 (1.54–2.21)	<0.001	1.63 (1.35–1.97)	<0.001	1.54 (1.27–1.87)	<0.001
Wheezing						
Sleep duration (h)						
7–8	1(Ref)		1(Ref)		1(Ref)	
<7	1.41 (1.26–1.58)	<0.001	1.26 (1.11–1.42)	<0.001	1.21 (1.07-1.37)	0.003
>8	1.17 (0.92–1.50)	0.205	1.13 (0.86–1.49)	0.361	1.08 (0.82–1.41)	0.587
Dyspnea						
Sleep duration (h)						
7–8	1(Ref)		1(Ref)		1(Ref)	
<7	1.51 (1.41–1.63)	<0.001	1.46 (1.31–1.62)	<0.001	1.39 (1.25–1.55)	<0.001
>8	1.48 (1.30–1.68)	<0.001	1.28 (1.08–1.52)	0.006	1.17 (0.98–1.40)	0.076

Model 1 adjusted nothing, model 2 was adjusted for age, sex, race, BMI, smoking, and model 3 was adjusted for model 2 plus education, cardiovascular disease, diabetes, and hypertension.

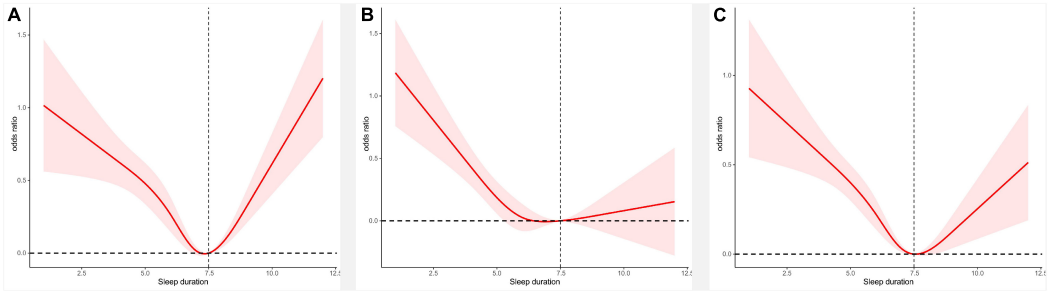

FIGURE 1
Panel **(A)** shows the curves of sleep duration and cough, panel **(B)** shows the curves of sleep duration and wheeze, and panel **(C)** shows the curves of sleep duration and dyspnea.

stratified analysis. The results in Table 3 support a U-shaped relationship between sleep duration and respiratory symptoms. Sleep duration was negatively correlated with cough (HR 0.80,95% CI 0.73–0.87) and dyspnea (HR 0.82,95% CI 0.77–0.88) before 7.5 h, whereas after >7.5 h, sleep duration was positively correlated with cough (HR 1.30,95% CI 1.14–1.48) and dyspnea (HR 1.12,95% CI 1.00–1.26). Supplementary Tables 1, 2 show the results before interpolation, in agreement with the main results.

Figure 1B shows the relationship between the curve of sleep duration and wheezing. Table 3 confirms a 13% reduction in the probability of wheezing occurring for each 1 h increase in sleep duration until 7.5 h. When >7.5 h, there was no statistical relationship between sleep duration and wheezing. In addition, Supplementary Table 3 shows that less sleep time is associated with COPD and asthma. Supplementary Table 4 shows that odds of coughing, wheezing, and dyspnea were higher in patients with sleep disorders. Supplementary Table 5 shows the results of the stratified analysis. As shown in Supplementary Figure 5, the relationship between sleep duration and respiratory symptoms was consistent with the primary results.

Discussion

Our study found an association between sleep duration and cough, wheezing, and dyspnea. We found a u-shaped relationship between sleep duration and cough and dyspnea by fitting curves and stratified regression. It was negatively correlated with cough and dyspnea when sleep duration was less than 7.5 h, while this relationship was positively correlated when sleep duration was greater than 7.5 h. Shorter sleep duration increases the incidence of wheezing. In addition to respiratory symptoms, we found that less sleep duration was associated with asthma and COPD.

Cough, wheezing, and dyspnea are significant complaints and are often considered to be related to cardiopulmonary disease. These respiratory symptoms not only increase the risk of death due to lung disease, but are also associated with cardiovascular mortality and all-cause mortality (2, 17, 18). In addition, respiratory symptoms were an independent predictor of reduced lung function, COPD, and asthma (19–21).

Several studies have found a relationship between various sleep disorders and respiratory symptoms (22, 23). More respiratory symptoms were also present in people with habitual snoring (24).

TABLE 3 Stratified regression of sleep duration and respiratory symptoms.

Inflection point of sleep duration (7.5 h)	OR (95% CI)	*P*
Cough		
Sleep duration (h) <7.5	0.80 (0.73–0.87)	<0.001
Sleep duration (h) ≥7.5	1.30 (1.14–1.48)	<0.001
P for interaction		<0.001
Wheezing		
Sleep duration (h) <7.5	0.85 (0.79–0.92)	<0.001
Sleep duration (h) ≥7.5	1.07 (0.92–1.23)	0.378
P for interaction		0.005
Dyspnea		
Sleep duration (h) <7.5	0.82 (0.77–0.88)	<0.001
Sleep duration (h) ≥7.5	1.12 (1.00–1.26)	0.047
P for interaction		<0.001

Adjusted for age, sex, race, BMI, smoking, education, cardiovascular disease, diabetes, and hypertension.

Bjornsdottir found that people with short sleep times reported more respiratory symptoms; not only that, they found that long sleep duration was associated with morning cough and dyspnea after activity (25). Unlike Bjornsdottir's study, we did not identify a correlation between long sleep and dyspnea. This difference may be related to the definition of the length of sleep. Therefore, we were more interested in a linear relationship. We discovered a U-shaped association between sleep duration and cough and dyspnea, with the inflection point for optimal sleep duration being about 7.5 h.

The health hazards of sleep deprivation are well known, but the dangers of excessive sleep are easily overlooked (9). Study shows excessive sleep is an independent risk factor for metabolic syndrome, obesity, and depression (26–28). Long periods of sleep can also be potentially harmful (29). A meta-analysis showed that excessive sleep rather than less sleep duration was associated with increased systemic inflammatory biomarkers (CRP and IL-6) (30). Two studies show a U-shaped relationship between sleep and FeNO and lung function (31, 32). Several of the above studies help explain the curvilinear relationship between sleep, cough, and dyspnea.

In addition to respiratory symptoms, we found that short sleep duration was associated with asthma and COPD. Another study on NHANES also confirmed the association between less sleep duration and asthma (32). Among asthmatics, short sleep duration asthma attacks are more frequent, and long sleep duration people have more frequent activity limitations (33). Shorter sleep time is associated with the development of COPD and is an essential factor in the quality of life of COPD patients (34, 35). Adults with chronic airway obstructive disease are more likely to have sleep disorders (36). Given the association between sleep and respiratory disease, we performed additional subgroup analyses. In people without asthma and COPD (S4), sleep duration still has a U-shaped relationship with cough and dyspnea.

The current study has several advantages; professional data collection standards ensure accurate data. In addition, the data characteristics of the sample can reflect the characteristics of the overall U.S. population by weighting. Admittedly, our study has some limitations. First, the characteristics of the cross-sectional study led us not to determine the causal relationship between sleep duration and coughing, wheezing, and dyspnea. Second, self-reported sleep duration may not be as accurate as polysomnography. Third, we lacked factors regarding sleep duration and respiratory symptoms, such as sleep apnea, GERD, sleep quality, and insomnia. Forth, the diagnosis of COPD and asthma rely on patient self-report, which may create a potential bias. Finally, this was an analysis conducted in subjects greater than or equal to 40 years of age and the results do not generalize to those younger than 40 years of age.

Conclusion

In conclusion, this research revealed a U relationship between sleep duration, cough, and dyspnea. And short sleep duration is also a risk factor for wheezing, asthma, and COPD. This finding provides new insights into the management of respiratory symptoms and diseases. In the future, more studies are needed to fully analyze all aspects of sleep (duration, quality) with respiratory symptoms (cough, wheezing, dyspnea) to understand more clearly about this relationship.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

Study protocols for NHANES were approved by the NCHS Ethics Review Board (Protocol #2011–17, https://www.cdc.gov/nchs/nhanes/irba98.htm). All the participants signed the informed consent before participating in the study. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZR and DL participated in the study design and edited the manuscript. ZR, DL, and XMC participated in the extraction and cleaning of data, and carried out the visualization analysis of the data. XMC, YL, and MJ participated in manuscript modification. ZQ and XHC participated in the research design and editor of the manuscript. All authors reviewed and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1108663/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Flow chart of the study.

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Mental health and sleep quality among patients with asthma and COPD

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This study aims to compare the mental health of patients with asthma and COPD in terms of anxiety, depression, and sleep quality and to examine the factors that predict sleep disturbance, anxiety, and depressive symptoms.

Methods: This quantitative cross-sectional study employed convenience sampling to enroll 200 patients with asthma and 190 patients with COPD. Data were gathered using a standardized self-administered questionnaire that contained sections on patients' characteristics, the Sleep Quality, Anxiety, and Depression.

Results: The prevalence of poor sleep quality was 17.5 and 32.6% among asthmatic and COPD patients, respectively. The incidence of anxiety and depression was 38 and 49.5% among the patients with asthma, respectively. Their prevalence in patients with COPD was 48.9 and 34.7%, respectively. The multivariate regression analysis showed that marital status (married), BMI, education level (pre-university level), presence of comorbid illness, and depression were significant predictors of PSQI in asthmatic patients. Moreover, age, gender (male), marital status (married), education level (pre-university level), depression, and anxiety were significant predictors of PSQI among COPD participants. According to this study, COPD, and asthma pose serious health risks, including reduced sleep quality, anxiety, and depression.

KEYWORDS

chronic obstructive pulmonary disease (COPD), asthma, sleep disturbance, anxiety, depression

1. Introduction

Chronic respiratory disorders account for 10% (4.1 million) of non-communicable disease mortality, and 74% (40 million) of all fatalities (1). Two of the most prevalent chronic lung diseases worldwide are asthma and chronic obstructive pulmonary disease (COPD) (2). Asthma and COPD are also the most prevalent serious illnesses in Saudi Arabia, and local reports indicate that these conditions are becoming more prominent (3). As the industrialization and modernity of the last ten years have increased, so has the prevalence of asthma. According to the World Health Organization (WHO), there were over 383,000 asthma-related deaths in 2015, affecting 235 million people worldwide (4). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) asserts that COPD is a prevalent, curable condition (5). Over the following 10 years, COPD is anticipated to overtake all other significant causes of mortality as the third leading cause of death worldwide (5). In 2019, there were 3.9 million mortalities and an estimated 455 million cases of COPD (6).

More than 2 million Saudis suffer from asthma, and most of them have uncontrolled asthma, which negatively influences their quality of life. According to the Saudi Arabian (SA) Ministry of Health, 15–25% of people in SA have asthma (1). Despite improvements in modern medicine, 40–70% of people still have uncontrolled asthma (7). In addition, an epidemiological study that sought to determine the prevalence and incidence of COPD in Saudi Arabia from 1990 to 2019 found that the number of instances of the disease was rising: from 1,381.26 (1,285.35–1,484.96) cases per 100,000 people in 1990 to 2,053.04 cases per 100,000 people in 2016 (1918.06–2194.29) (8).

Patients with asthma and COPD experience significant impairments in their physical and mental health, which considerably impair their performance in day-to-day activities and social interactions and raise their risk of morbidity and mortality (9). In addition, asthma, and COPD are both prevalent, not fully curable diseases typically characterized by a slowly progressing and persistent airflow restriction that may cause sleep disturbances (1). The symptoms of sleep disorders that can interfere with daytime activities include the inability to maintain a high level of sleep quality or problems with sleep duration. Patients with asthma frequently complain of sleep disruptions, including early morning awakenings and trouble falling or staying asleep (3, 4, 7, 8).

Previous researches suggest a relationship between sleep quality and mental health among individuals with COPD and asthma. Sleep disorders are correlated with the severity of asthma, and sleep quality in COPD patients is an essential determinant of quality of life (9, 10). Centers for Diseases Control and prevention reported that mental and physical health are equally important components of overall health, and mental health includes emotional, psychological, and social well-being (11). In addition, there is a close association between mental health and respiratory diseases. For instance, patients with COPD and asthma are more likely to experience anxiety and depression (12, 13).

Asthma and depression are linked, and depression has been linked to sleep disorders, poor sleep quality, and lower quality of life (14). Compared to the general population, patients with asthma and COPD have approximately three times the prevalence of sleep disruption, anxiety, and depression. Therefore, asthma, and COPD treatments should include early diagnosis and multi-modal therapy for sleep disruption, anxiety, and depression (15). However, to date, few studies have investigated the predictors of asthma and COPD. This study compared the mental health of patients with asthma and COPD in terms of anxiety, depression, and sleep quality. In addition, the current research examines the factors that predict sleep disturbance, anxiety, and depressive symptoms in individuals with asthma and COPD.

2. Materials and methods

2.1. Setting and design

The study was carried out in primary healthcare facilities with smoking and respiratory clinics in Alhufof, in the eastern Saudi Arabian province of Al-Ahsa. To achieve the study's objectives, a quantitative cross sectional research design was used.

2.2. Participants

A convenience sampling of 200 asthma patients and 190 COPD patients was conducted. The eligible criteria were: both gender, age > 18 years, stable health status, verbal, and cognitive ability, absence of mental illnesses, and agreement to participation. Clinical history, physical examination, and spirometry were used in our research setting to diagnose asthma following the Global Initiative for Asthma (GINA) guidelines. In addition, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, spirometry is the gold standard for diagnosing COPD, therefore, only those patients diagnosed by their physician based on their spirometry results were included. Exclusion criteria included patients with malignancy, acute or exacerbations of respiratory conditions, and patients whose diagnoses had not been verified were excluded. In addition, all patients had to be clinically stable, meaning they experienced no exacerbation in the four weeks before recruitment.

2.3. Data collection

Data were gathered using a standardized self-administered questionnaire. It contained two standardized tools and a section on patient characteristics, such as age, gender, marital status, degree of education, BMI, respiratory disease in the family, smoking history, and comorbid illness.

The Sleep Quality Pittsburgh Sleep Quality Index (PSQI) was used to evaluate subjective sleep problems over a one-month period (16). This is a standardized questionnaire, and previous research has evaluated and confirmed its validity and reliability for the Arab community (17, 18). Therefore, the Arabic version was chosen for our study (19). The PSQI is a 19-item self-rating scale that assesses the perceived quality of sleep for a previous month. It includes seven domain ratings for subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disruptions, the use of sleeping medications, and daytime dysfunction. A higher score denotes poorer sleep quality, and each item is weighted on a 0–3 scale. Global ratings are based on a scale of 0 to 21, with a score of five or more indicating bad sleep and a score of five or less indicating good sleep (16).

The Hospital Anxiety and Depression Score (HADS), a self-report test used frequently in non-psychiatric settings to assess the two most common expressions of distress—anxiety and depression—was the second tool. The HADS consists of seven questions each for anxiety and depression. Each item is scored on a four-point scale, with 0 denoting "not present" and 3 denoting a "considerable event." The total score on these two subscales ranges from 0 to 21. The threshold score is eight or higher. A score of eight or more on the depression and anxiety subscales is regarded as symptomatic or an atypical condition. The HADS has a specificity of 0.78 and a sensitivity of 0.9 for anxiety and a specificity of 0.79 and a sensitivity of 0.83 for depression (20, 21). The Arabic version was used. Cronbach's alpha for the HADS depression and anxiety subscales was 0.77 (0.7–0.83) and 0.83 (95% confidence interval: 0.79–0.88), respectively (22).

Five patients participated in a pilot research to evaluate the tool's visibility, filling speed, and usefulness. Each participant was examined by the researchers in light of the above-mentioned inclusion criteria

as well as the objectives and aims of the study. Those who agreed to participate were then asked to sign an informed consent form and complete the questionnaire. The questionnaire was completed in 10 to 15 min by each participant. The data collection took approximately 6 months, between October 2021 and March 2022.

2.4. Ethical considerations

The Research and Ethical Committee, Ministry of Health, authorized the research proposal (approval number IRB KFHH no. H-05-HS-065). After outlining the purpose of the study, the patients gave their informed consent. Participation in this study was entirely voluntary. The patient's confidentiality, privacy, anonymity, and right to withdraw from the study at any time were guaranteed. The Declaration of Helsinki (23) was observed, and ethical guidelines were followed when conducting the study.

2.5. Statistical analysis

Version 28 of the SPSS (Statistical Package for the Social Sciences) software was used to collect and analyze the data. The results of the descriptive statistics were given as a number (%) or mean (SD) for the categorical and continuous variables, respectively. The data's normality was analyzed graphically. The PSQI and depression and anxiety were correlated using Pearson's correlation coefficient. In order to determine which patient features were highly predictive of insufficient sleep, sadness, and anxiety, numerous linear regression analyses were conducted. With a 95% confidence interval, a p value of 0.05 was deemed significant. To account for all factors, we also performed multivariate linear regressions.

3. Results

Table 1 shows that 200 patients with asthma and 190 patients with COPD were enrolled in the current study. The mean (SD) ages of the patients with asthma and patients with COPD were 36.23 ± 10.19 years and 47.06 ± 10.91, respectively. Most patients in the asthma group (77%) were female (58.5%), while 61.1% of patients in the COPD group were male. The majority of the study participants had no history of previous hospital admissions.

Table 2 shows the frequency of the PSQI elements. The frequency of poor sleep quality was 17.5 and 32.6% among the asthma and COPD groups, respectively. More than half of the participants reported sleeping fairly well. About 34.5% in the asthma group had sleep latency of 16–30 min, while 36.3% in the COPD group had 31–60 min of sleep latency. About 59.5% of the asthma group and 71.1% of the COPD group informed sleep disturbances at least once per week. Furthermore, more than 50% of study participants claimed to have daytime dysfunction, and the majority of patients in both asthma and COPD groups did not use sleep medications.

Table 3 shows the prevalence of depression and anxiety was 49.5 and 38% among patients with asthma, respectively. In COPD patients, the prevalence was 48.9 and 34.7%, respectively.

Table 4 shows the factors of poor sleep quality among patients with asthma and COPD.

TABLE 1 Distribution of characteristics of patients with asthma (N =200) and COPD (N =190).

Characteristics	Patient with asthma	Patient with COPD
	N (%) Mean SD	N (%) Mean SD
Age	36.23 ± 10.19	47.06 ± 10.91
Gender		
Male	46 (23.0)	116 (61.1)
Female	154 (77.0)	74 (38.9)
Marital status		
Single	86 (43.0)	79 (41.6)
Married	114 (57.0)	111 (58.4)
Education level		
Pre-university	153 (76.5)	131 (68.9)
University level	47 (23.5)	59 (31.1)
BMI		
Normal	59 (29.5)	4 (2.1)
Overweight	138 (69.0)	46 (24.2)
Obese	3 (1.5)	140 (73.7)
Family history of respiratory diseases		
Yes	31 (15.5)	17 (8.9)
No	169 (84.5)	173 (91.1)
Smoking (lifetime)		
Yes	24 (12.0)	141 (74.2)
No	176 (88.0)	49 (25.8)
Previous hospital admission for exacerbation		
Yes	48 (24.0)	15 (7.9)
No	152 (76.0)	175 (92.1)
Comorbid illness		
None	153 (76.5)	141 (74.2)
Anemia	14 (7.0)	9 (4.7)
Hypertension	22 (11.0)	24 (12.6)
Diabetes Mellitus	8 (4.0)	16 (8.4)
Dysrhythmia	3 (1.5)	0 (0)

In patients with asthma, the univariate linear regression model showed that the predictors of poor sleep quality were age, marital status (married), education level (pre-university level), presence of comorbid illness, and depression. These were independently associated with worse sleep quality. In the multivariate regression model, marital status (married), BMI, education level (pre-university level), presence of comorbid illness, and depression were the significant predictors of PSQI.

In patients with COPD, the univariate linear regression model showed that the predictors for poor sleep quality were age, gender (male), marital status (married), family history of the disease (no), education level (pre-university level), presence of comorbid illness, and anxiety independently associated with worse sleep quality. In the multivariate regression model, age, gender (male), marital status (married), education level (pre-university level), depression, and

TABLE 2 Frequency of PSQI elements of participants with asthma (*N* =200) and COPD (*N* =190).

Elements	Asthma *N* (%)	COPD *N* (%)
Subjective sleep quality		
Very good	46 (23.0)	54 (28.4)
Fairly good	110 (55.0)	122 (64.2)
Fairly bad	29 (14.5)	14 (7.4)
Very bad	15 (7.5)	0 (0)
Sleep latency		
<15 min	24 (12.0)	22 (11.6)
16–30 min	69 (34.5)	59 (31.1)
31–60 min	55 (27.5)	69 (36.3)
>60 min	52 (26.0)	40 (21.1)
Sleep duration		
>7 h	55 (27.5)	41 (21.6)
6–7 h	60 (30.0)	53 (27.9)
5–6 h	34 (17.0)	58 (30.5)
<5 h	51 (25.5)	38 (20.0)
Sleep efficiency		
>85%	129 (64.5)	99 (52.1)
75–84%	35 (17.5)	51 (26.8)
65–74%	21 (10.5)	17 (8.9)
<65%	15 (7.5)	23 (12.1)
Sleep disturbance		
Not in the previous month	0 (0)	0 (0)
Less than once a week	119 (59.5)	135 (71.1)
Once or twice a week	81 (40.5)	55 (28.9)
Three or more times a week	0 (0)	0 (0)
Use of sleep medication		
Not during past month	140 (70.0)	157 (82.6)
Less than once per week	34 (17.0)	18 (9.5)
Once or twice a week	26 (13.0)	8 (4.2)
At least three times every week	0 (0)	7 (3.7)
Daytime dysfunction		
Not during past month	56 (28.0)	107 (56.3)
Less than once a week	54 (27.0)	51 (26.8)
Once or twice a week	81 (40.5)	25 (13.2)
Three or more times a week	9 (4.5)	7 (3.7)
Good Sleep Quality (<4)	165 (82.5)	128 (67.4)
Poor Sleep Quality(>5)	35 (17.5)	62 (32.6)

anxiety were significant predictors of PSQI for COPD patients, as shown in Table 4.

Table 5 displays that age, gender, marital status, education level (pre university level), and anxiety were all independent predictors of a higher level of depression in patients with asthma. In patients with COPD, BMI, family history of respiratory disease, smoking, pre-university education level, prior hospital admission, prior dyspnea, and anxiety were the factors that independently predicted an escalating level of depression.

TABLE 3 Frequency of anxiety and depression among patients with asthma (*N* =200) and COPD (*N* =190).

Variable	*N* (%)	
Depression (Total Score)	**Asthma**	**COPD**
Normal (0–7)	101 (50.5)	97 (51.1)
Abnormal (8–21)	99 (49.5)	93 (48.9)
Anxiety (Total Score)		
Normal (0–7)	124 (62.0)	124 (65.3)
Abnormal (8–21)	76 (38.0)	66 (34.7)

Moreover, BMI, family history of respiratory disease, previous hospital admission, the presence of comorbidities, dyspnea within the past month, and depression were the factors that independently predicted a higher level of anxiety among asthmatic patients. However, among COPD patients, factors such as male gender, family history of respiratory disease, smoking, pre-university education level, presence of comorbidities, dyspnea within the past month, and depression were associated with higher levels of anxiety.

Table 6 shows that there is correlation between sleep quality, anxiety, and depression among patients with asthma and COPD (*N* = 390).

4. Discussion

A significant sample size of asthma and COPD patients was used in the study to explore the prevalence of mental health problems and poor sleep quality, in Al-Ahsa, Saudi Arabia. Poor sleep, depression, and anxiety were somewhat common in this patient group, and a variety of factors contributed to this frequency. Healthcare providers should therefore be alert to these disorders and address them promptly and effectively.

Research on the prevalence of poor sleep quality in the Saudi population is lacking, despite the fact that the prevalence of poor sleep quality in patients with respiratory illnesses has been extensively studied in the literature. In our study, we found that poor sleep quality has a higher incidence among patients with COPD than among those with asthma (32.6% vs. 17.5%), as measured by the PSQI. Asthmatics had longer sleep duration, efficiency, and latency, whereas COPD patients had better sleep quality, fewer sleep disturbances, and used fewer sleep medications than asthmatics. This is consistent with a study (24) that found that the PSQI scores for COPD were higher than those for asthma. In contrast, our study found that COPD patients had longer sleep latency and used sleep-regulating medications more often. The disparity in the reported prevalence of sleep components is probably due to methodological variations, such as sample size and study design. Our findings also support a study (25) that reported a 35% (*N* = 245) incidence of poor sleep quality in patients with chronic respiratory diseases Furthermore, another study (26) reported that more than half (53% of 1,117) of the participants with COPD reported "poor" sleep quality.

With sleep occupying up to one-third of every adult's life, addressing sleep is essential to overall health. Sleep disturbances and deficiencies are common in patients with chronic lung diseases and

TABLE 4 Regression analyses of poor sleep quality based on the characteristics of patients with asthma (N =200) and COPD (N =190).

	Asthma				COPD			
Independent variables	Univariate model: β (95% CI)	p	Multivariate model: β (95% CI)	p	Univariate model: β (95% CI)	p	Multivariate model: β (95% CI)	p
Age	0.009 (0.003, 0.014)	0.001	0.004 (−0.002, 0.010)	0.206	−0.014 (−0.020, −0.008)	<0.001	−0.009 (−0.015, −0.003)	0.002
Gender (Male)	0.083 (−0.043, 0.209)	0.194	0.119 (−0.014, 0.252)	0.080	0.180 (0.044, 316)	0.010	0.271 (0.134, 0.408)	<0.001
Marital status (married)	0.203 (0.099, 0.307)	<0.001	0.110 (−0.004, 0.224)	0.059	0.330 (0.201, 0.458)	<0.001	0.267 (155, 0.379)	<0.001
BMl	−0.060 (−0.171, 0.050)	0.281	−0.111 (−0.218, −0.004)	0.042	−0.013 (−0.149, 0.123)	0.847	0.096 (−0.020, 0.211)	0.106
Family history of the disease (no)	−0.016 (−0.163, 0.131)	0.828	−0.120 (−0.281, 0.040)	0.142	−0.358 (−0.589, −0.128)	0.002	−0.159 (−0.387, 0.068)	0.169
Smoking (lifetime) (no)	−0.009 (−0.173, 0.154)	0.909	0.014 (−0.146, 0.175)	0.860	0.082 (−0.072, 0.236)	0.293	−0.118 (−0.259, 0.024)	0.103
Education level (pre-university level)	−0.188 (−0.311, −0.066)	0.003	−0.278 (−0.403, −0.153)	<0.001	−0.166 (−0.310, −0.022)	0.024	−0.161 (−0.305, −0.016)	0.029
Previous hospital admission (no)	−0.066 (−0.190, 0.059)	0.298	−0.212 (−0.349, −0.075)	0.003	−0.065 (−0.315, 0.185)	0.610	−0.168 (−0.457, 0.121)	0.253
Comorbid illness (yes)	0.087 (0.032, 0.142)	0.002	0.104 (0.046, 0.162)	<0.001	−0.061 (−0.128, 0.005)	0.071	−0.072 (−0.132, −0.013)	0.018
Dyspnea last month (no)	−0.048 (−0.154, 0.059)	0.379	0.080 (−0.033, 0.193)	0.166	−0.233 (−0.364, −0.102)	0.001	−0.093 (−0.258, 0.072)	0.267
Depression (yes)	0.247 (0.146, 0.347)	<0.001	0.175 (0.068, 0.282)	0.001	−0.035 (−0.170, 0.100)	0.611	−0.378 (−0.527, −0.228)	<0.001
Anxiety (yes)	0.070 (−0.039, 0.179)	0.208	0.053 (−0.058, 0.164)	0.350	0.337 (0.204, 0.471)	<0.001	0.433 (0.269, 0.598)	<0.001

Model R-square of participants with asthma = 0.299, value of $p < 0.001$. Model R-square of participants with COPD = 0.471, value of $p < 0.001$.

are associated with worse clinical outcomes and poor quality of life (27). The causes of poor sleep quality in patients with asthma and COPD remains unclear. However, a variety of considerations have been proposed. A prior study (28) demonstrated a significant correlation between respiratory problems and insufficient sleep. Patients with asthma and COPD frequently encounter symptoms, such as coughing, shortness of breath, dyspnea, and wheezing. These symptoms have been linked to higher rates of insomnia and daytime sleepiness than people who do not exhibit them. Dyspnea, a defining feature of COPD, secretion buildup along with mucus clogging the airways, poor ventilation and inadequate oxygenation have all been found to significantly impact sleep quality (29, 30).

Patients with chronic lung diseases frequently experience mental health problems as anxiety and depression, which have a serious impact on their health and prognosis. According to a randomized cross-sectional study (31) conducted in Sharurah, Saudi Arabia, 12% of 280 patients evaluated in primary healthcare facilities were diagnosed with depression. In the present study, we found the prevalence of depression and anxiety to be 49.5 and 38% vs. 48.9 and 34.7% among patients with asthma vs. patients with COPD, respectively. We also found that the prevalence of depression was nearly the same in both patients with asthma and COPD (49.5% vs. 48.9%), whereas the prevalence of anxiety was higher in patients with asthma than in patients with COPD (38% vs. 34.7%). Consistent with our results, a study (32) estimated that 70% of asthmatic patients have experienced some degree of anxiety. Symptoms of their condition and their fear of suffocation make asthma patients more likely to experience moderate levels of anxiety. This is contradicted by the findings of another study (33) that found mild depression in both asthma and COPD and that patient with asthma had moderate levels of anxiety while patients with COPD had high levels of anxiety.

For individuals with chronic respiratory conditions, the quality of their sleep is crucial to their physical and mental health (34). In the current study, individuals with COPD experienced poorer sleep quality more than those with asthma. This can be explained by the fact that COPD participants did not use sleeping aids in the previous month, and they experienced sleep disturbances "less than once a week." This is consistent with a previous study (35) in which majority (94% of 51) of the patients with COPD reported "poor" sleep quality. According to a study (36), "getting up to use the bathroom" was the most frequent cause of sleep disruption. The multivariate regression analysis in our study showed that marital status (married), education level (pre-university level), and depression were significant predictors of PSQI among both asthmatic and COPD participants.

TABLE 5 Regression analysis of depression and anxiety scores based on the characteristics of patients with asthma (*N* =200) and COPD (*N* =190).

	Depression							
	Asthma				COPD			
Independent variables	Univariate model: β (95% CI)	*p*	Multivariate model: β (95% CI)	*p*	Univariate model: β (95% CI)	*p*	Multivariate model: β (95% CI)	*p*
Age	0.018 (0.011, 0.024)	<0.001	0.018 (0.010, 0.026)	<0.001	0.000 (−0.006, 0.007)	0.930	0.003 (−0.002, 0.009)	0.217
Gender (Male)	−0.232 (−0.396, −0.069)	0.006	−0.245 (−0.42-, −0.070)	0.006	−0.071 (−0.218, 0.076)	0.340	−0.097 (−0.231, 0.037)	0.156
Marital status (Married)	0.297 (0.162, 0.432)	<0.001	0.101 (−0.052, 0.254)	0.195	0.079 (−0.066, 0.225)	0.282	−0.015 (−0.126, 0.096)	0.788
BMl	−0.028 (−0.173, 0.118)	0.708	−0.054 (−0.198, 0.090)	0.457	0.031 (−0.114, 0.176)	0.677	0.116 (0.003, 0.229)	0.045
Family history of the respiratory disease (Yes)	0.051 (−0.142, 0.245)	0.601	0.012 (−0.204, 0.229)	0.910	0.085 (−0.166, 0.337)	0.504	0.304 (0.084, 0.524)	0.007
Smoking(lifetime) (No)	−0.006 (−0.221, 0.210)	0.959	0.163 (−0.052, 0.378)	0.137	−0.110 (−0.273, 0.054)	0.188	−0.138 (−0.276, 0.001)	0.051
Education level (Pre-university level)	−0.119 (−0.283, 0.046)	0.156	−0.211 (−0.377, −0.046)	0.013	−0.267 (−0.418, −0.117)	0.001	−0.317 (−0.452, −0.182)	<0.001
Previous hospital admission (No)	−0.007 (−0.171, 0.157)	0.937	−0.083 (−0.267, 0.101)	0.376	−0.410 (−0.670, −0.149)	0.002	−0.559 (−0.833, −0.286)	<0.001
Comorbid illness (Yes)	0.025 (−0.049, 0.099)	0.505	−0.007 (−0.085, 0.071)	0.854	0.071 (0.000, 0.142)	0.049	0.002 (−0.057, 0.061)	0.949
Dyspnea last month (No)	−0.161 (−0.299, −0.022)	0.023	−0.058 (−0.210, 0.094)	0.451	−0.580 (−0.697, −0.462)	<0.001	−0.366 (−0.520, −0.213)	<0.001
Anxiety (Yes)	0.178 (0.036, 0.320)	0.014	0.190 (0.043, 0.337)	0.012	0.620 (0.498, 0.742)	<0.001	0.288 (0.131, 0.445)	<0.001
Anxiety								
Age	0.012 (−0.011, 0.002)	0.215	−0.005 (−0.012, 0.003)	0.221	−0.005 (−0.011, 0.001)	0.129	0.000 (−0.005, 0.006)	0.894
Gender (Male)	−0.099 (−0.260, 0.062)	0.225	−0.042 (−0.214, 0.130)	0.631	−0.038 (−0.178, 0.103)	0.596	−0.259 (−0.379, −0.139)	<0.001
Marital status (Married)	0.075 (−0.062, 0.212)	0.281	−0.016 (−0.165, 0.134)	0.837	0.140 (0.002, 0.277)	0.047	0.046 (−0.058, 0.150)	0.381
BMl	−0.210 (−0.348, −0.072)	0.003	−0.151 (−0.290, −0.012)	0.034	−0.005 (−0.143, 0.133)	0.941	0.001 (−0.105, 0.107)	0.986
Family history of the disease (Yes)	0.259 (0.074, 0.443)	0.006	0.367 (0.367, 0.572)	0.001	−0.071 (−0.311, 0.169)	0.561	−0.200 (−0.405, 0.004)	0.055
Smoking(lifetime) (No)	−0.042 (−0.251, 0.168)	0.695	082 (−0.292, 0.129)	0.445	0.054 (−0.102, 0.211)	0.493	0.137 (0.009, 0.265)	0.037
Education level (Pre-university level)	0.032 (−0.129, 0.192)	0.697	0.152 (−0.008, 0.313)	0.063	−0.332 (−0.472, −0.192)	<0.001	−0.352 (−0.468, −0.237)	<0.001
Previous hospital admission (No)	0.226 (0.070, 0.382)	0.005	0.291 (0.116, 0.466)	0.001	−0.130 (−0.383, 0.124)	0.315	0.203 (−0.052, 0.457)	0.119
Comorbid illness (Yes)	0.108 (0.038, 0.179)	0.003	0.131 (0.057, 0.204)	0.001	0.087 (0.019, 0.154)	012	0.073 (0.019, 0.127)	0.009
Dyspnea last month (No)	−0.122 (−0.257, 0.013)	0.076	−0.342 (−0.482, −0.201)	<0.001	−0.572 (−0.682, −0.463)	<0.001	−0.630 (−0.740, −0.520)	<0.001
Depression (Yes)	0.178 (0.036, 0.320)	0.014	0.190 (0.043, 0.337)	0.012	0.620 (0.498, 0.742)	<0.001	0.288 (0.131, 0.445)	<0.001

For asthma participants: Model *R*-square for depression = 0.267, value of $p < 0.001$, Model *R*-square for anxiety = 0.248, value of $p < 0.001$. For COPD participants: (Model *R*-square for depression = 0.543, value of $p < 0.001$, Model *R*-square for anxiety = 0.554, value of $p < 0.001$).

TABLE 6 Correlation between sleep quality, anxiety, and depression among patients with asthma and COPD (*N* =390).

Variables		Correlation	*p*-value
Diagnosis: (asthma and COPD)	PSQI	0.175**	0.001
	Depression	0.006	0.913
	Anxiety	0.034	0.504
PSQI	Depression	0.128*	0.012
	Anxiety	226**	<0.001
Depression	Anxiety	0.374**	<0.001

**Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed).

The PSQI sleep quality score and the HADS depression and anxiety scores were shown to have a high positive association in the current study. This supports a prior study's finding that depression and sleep difficulty are related (37). Additionally, past research has indicated associations between sleep disruptions and both depression and anxiety levels in COPD patients, which is consistent with our findings (38).

Overall, the results of the current study indicate that depression, followed by anxiety and sleep disturbance, was the disorder that most affected people with COPD and asthma. According to the study's findings, anxiety was more common in asthmatic participants than in COPD patients, whereas the incidence of depression was about the same in both groups (49.5 and 48.9%). According to earlier research, 10–57% of individuals with chronic respiratory illnesses have anxiety, and 10–59% experience depression (39, 40). Compared to patients with other chronic diseases, individuals with COPD had a higher risk of anxiety and depression, according to earlier research (41, 42).

The results of our study, which show a direct connection between anxiety and depression, are in line with earlier research. According to estimates from other studies, 26–43% of COPD patients also struggle with depression. Further research has revealed that COPD patients with depression are more likely to experience anxiety than COPD patients without depression (43, 44). Therefore, routine evaluations of individuals with CRDs' mental health ought to take precedence.

The important features of the current study are the size of the sample and the inclusion of individuals with COPD and asthma who also had co-existing comorbidities, a novel strategy that was rare in earlier studies. However, there are certain limitations in this study. First, because the study was cross-sectional, no causality could be determined. Second, the subjectivity of the instruments used to collect data on sadness, anxiety, and sleep quality, because these data were self-reported and subjective. However, all individuals had recently received a COPD or asthma diagnosis from their doctors. Finally, we lack information on occupational status, which would add more information for future research. This study emphasizes the importance of routinely checking patients with asthma and COPD for poor sleep, depression, and anxiety, and it suggests developing therapies and/or management regimens improve their quality of life.

5. Conclusion

The study concluded that different degrees of sleep disturbance, anxiety, and depression are evident in people with asthma and COPD. While the frequency of depression was roughly the same in both groups, individuals with asthma had higher anxiety levels than those with COPD. It is important to properly evaluate the psychosocial needs of people with COPD and asthma. The mental health state of a person should be taken into account when treating an illness. According to this study, COPD, and asthma pose serious health risks, including reduced sleep quality, anxiety, and depression.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by The Research and Ethical Committee, Ministry of Health, authorized and approved the research proposal (approval number IRB KFHH no. H-05-HS-065). The patients/participants provided their written informed consent to participate in this study.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Physical therapy for sleep apnea: a smartphone application for home-based physical therapy for patients with obstructive sleep apnea

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Purpose: In this study, we described "PT for Sleep Apnea", a smartphone application for home-based physical therapy of patients with Obstructive Sleep Apnea (OSA).

Methods: The application was created in a joint program between the University of Medicine and Pharmacy at Ho Chi Minh City (UMP), Vietnam, and National Cheng Kung University (NCKU), Taiwan. Exercises maneuvers were derived from the exercise program previously published by the partner group at National Cheng Kung University. They included exercises for upper airway and respiratory muscle training and general endurance training.

Results: The application provides video and in-text tutorials for users to follow at home and a schedule function to assist the user in organizing the training program, which may improve the efficacy of home-based physical therapy in patients with Obstructive Sleep Apnea.

Conclusion: In the future, our group plans to conduct a user study and randomized-controlled trials to investigate whether our application can benefit patients with OSA.

KEYWORDS

obstructive sleep apnea, home-based physical therapy, smartphone application, physical therapy, respiratory muscle training

1. Introduction

Obstructive sleep apnea (OSA) is a type of sleep-related breathing disorder in the adult population. The operational definition of OSA is repeated upper-airway collapse and narrowing-induced apnea/hypopnea during sleep (1). Current estimates indicate that OSA affects 10–30% of the adult population worldwide, with higher prevalence in the male and the aging/aged population (1). The direct cause of apnea and hypopnea in OSA is the repeated collapse or narrowing of the upper airway during sleep. Thus, in theory, the problem of

apnea/hypopnea during sleep can be mitigated by preventing upper airway collapse. Recent studies suggest multiple factors contribute to the collapse of the upper airway during sleep, including anatomical and non-anatomical factors (2). Anatomical factors include excessive fat accumulation at the tongue base and neck muscles, having a longer upper airway, or having larger tonsils and adenoids (3–7). Whereas non-anatomical factors included weakness and inadequate responsiveness of intrinsic/extrinsic muscles of the tongue, low arousal threshold, or unstable respiratory control (8).

Current clinical management of OSA includes continuous positive airway pressure (CPAP), trans-oral surgery to remove excess soft tissue, mandibular advancement device (MAD), and oral-pharyngeal physical therapy (2). In these, CPAP is the most effective in preventing upper airway collapse regardless of the cause (2). However, the patient adherence to CPAP is less than optimal due to its cost and interference with sleep (2).

On the other hand, oral-pharyngeal physical therapy may mitigate the severity of sleep apnea by improving the tension, stiffness, and responsiveness of intrinsic/extrinsic muscles of the tongue and the muscles that control the movement of the soft palate, thus preventing the collapse of the upper airway (9–14). Our previous study has shown that a 12-week, hospital-based physical therapy program can significantly alleviate the symptoms of OSA (15). However, a significant limitation of hospital-based exercise is that the patient needs to physically move from home to the hospital, which may involve many factors that ultimately affect the patients' adherence (16). For example, patients with low mobility and social support may have no one to transport them to the hospital once a week to partake in the rehabilitation program. For various reasons, a home-based rehabilitation program is essential to many rehabilitation programs (17). Recent studies also showed that home-based rehabilitation programs could be as effective as one-on-one rehabilitation with a physical therapist (18–22). In addition, during the COVID-19 pandemic visiting the hospital to attend a rehabilitation program may be unnecessary in many places (23). However, a significant challenge of the home-based rehabilitation program is that the patient needs to perform the exercise without the on-site instruction of a physical therapist. Thus, in this study, we designed a smartphone application to provide step-by-step instruction and guidance to assist patients with OSA in performing home-based physical therapy programs.

2. Materials and methods

2.1. Exercise maneuvers used in this study

This smartphone application is created in a joint research program between the University of Medicine and Pharmacy at Ho Chi Minh City (UMP), Vietnam, and National Cheng Kung University (NCKU), Taiwan. This application is the first step in the study "Smartphone application of physical therapy for obstructive sleep apnea patients". Exercises maneuvers demonstrated in this application were derived from the exercise program previously published by the partner group at National Cheng Kung University (15). The exercise program included two parts: a portion of the upper airway and respiratory muscle exercise and a portion of general endurance exercise. The upper airway and respiratory muscle exercise program aimed to improve muscle strength and muscle tone for the intrinsic and extrinsic tongue muscles and respiratory muscles. Whereas general endurance exercises were directed at improving muscle tone and mobility of pharyngeal and soft tissue to improve airway closure during sleep. This program also aims at reducing accumulative fat in the oropharynx. A detailed description of the exercise program used in this study is summarized in the Supplementary material.

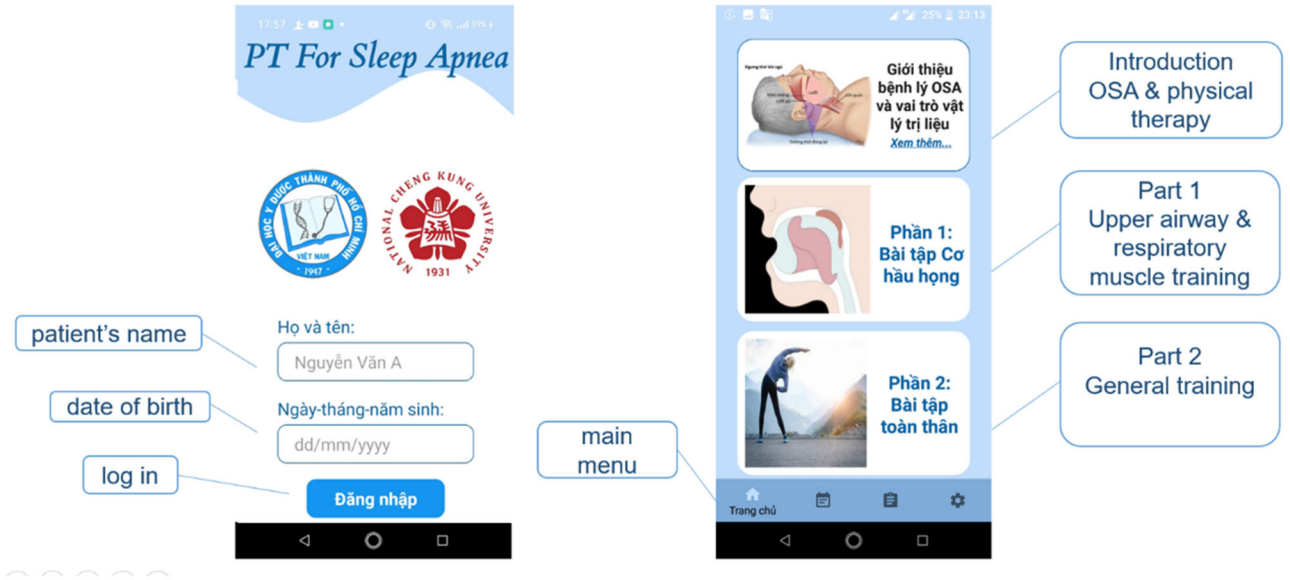

FIGURE 1
Log-in and home screen.

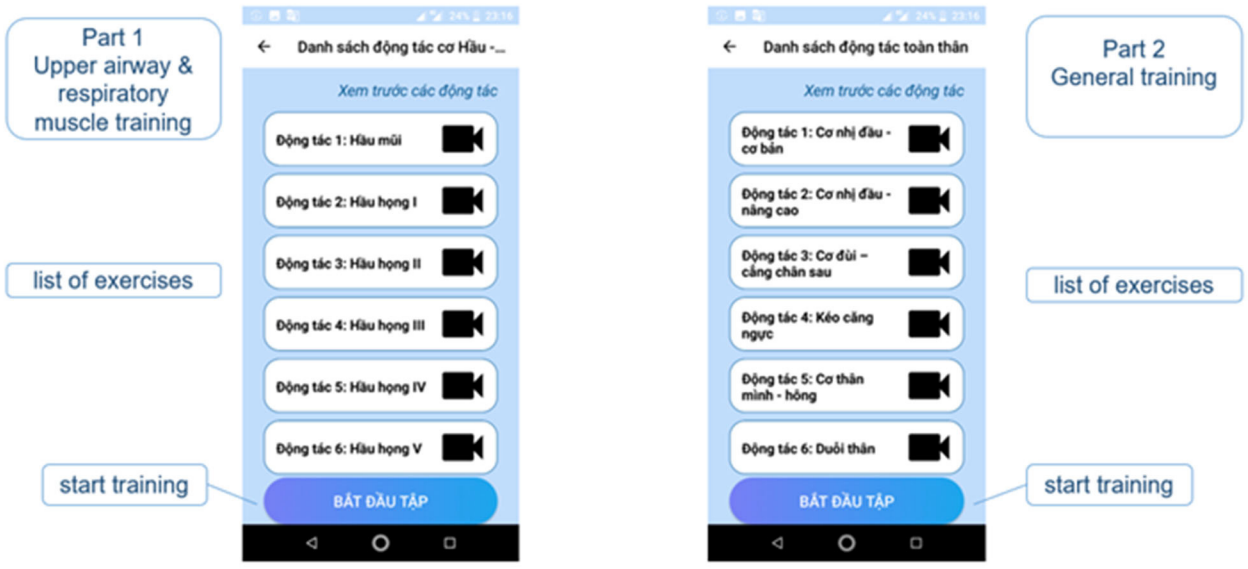

FIGURE 2
List of exercises.

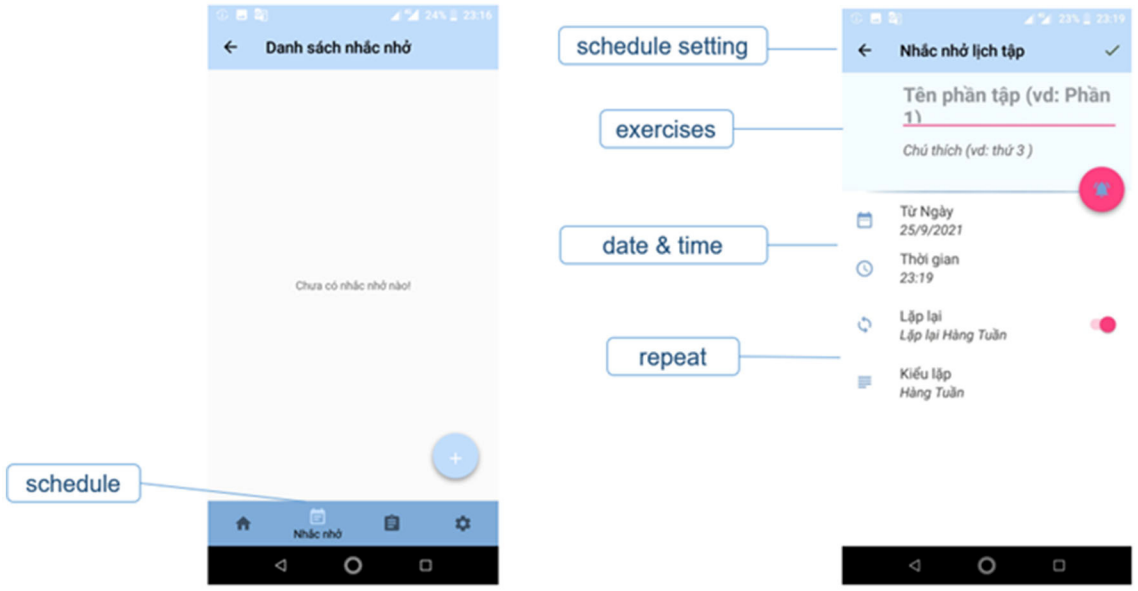

FIGURE 3
Schedule screen.

2.2. Architectural design

This app was designed by Medical AI Co., Ltd., Vietnam, with ideas and corrections by the UMP team. Currently, the language in this app is Vietnamese, and it is a prototype. It has been developed for the Android mobile operating system via Android Studio. This tool is an open-source platform initially introduced by Google as the official IDE for Android app development (24). Android Studio allows developers to design various creative applications written in the Java programming language. Android Studio includes perfect functions as well as libraries to develop an application, design user-interface, run emulators ["Android Virtual Devices (AVDs)], and build APK (Android Package) files easily. Furthermore, SQLite was chosen as a database server in this app, the most common database engine that is a serverless and self-contained database (25).

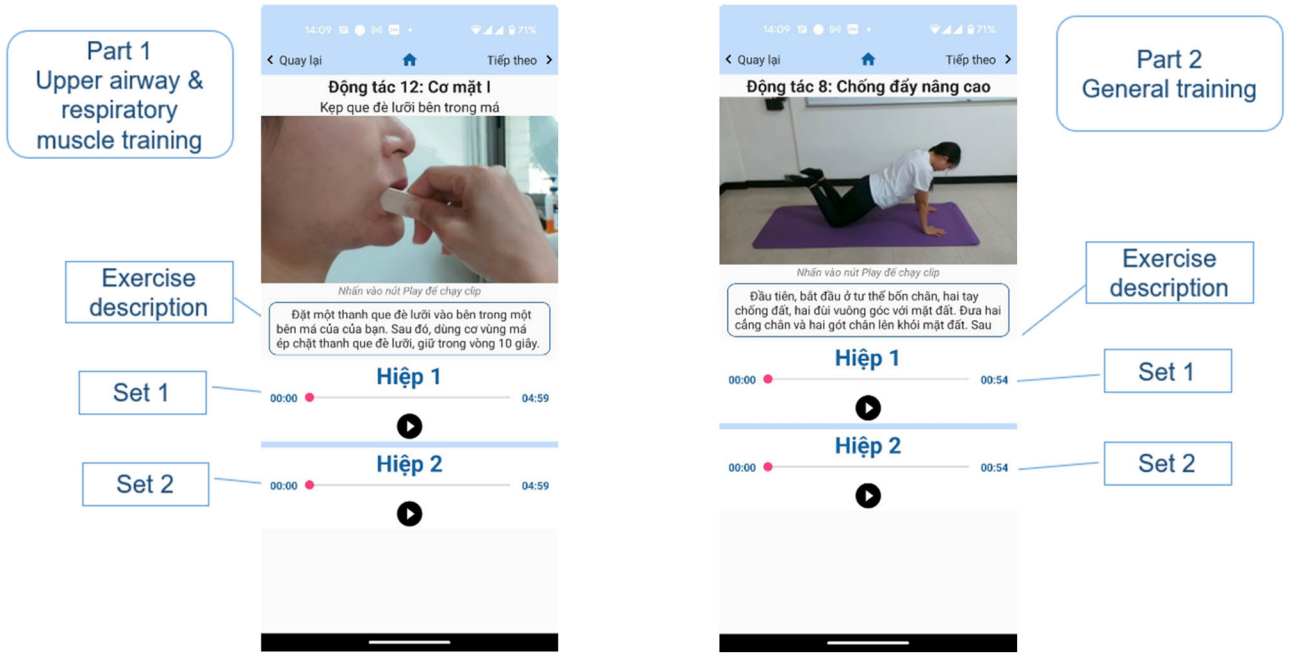

FIGURE 4
Training screen.

3. Results

3.1. User interface and contents

When the application starts, a login screen will ask the patients to fill in their Full name and "Date of Birth" login information. When the user enters the correct and sufficient information, then press the "Login" button to access the application's content. The toolbar at the bottom of the screen includes 4 main items: Home screen, Schedule, Diary, and Setting (Figure 1). The home screen (Figure 1) contains 3 main pieces of information: Introduction to OSA and the role of physiotherapy, tutorials for upper airway and respiratory muscle exercise, and tutorials for general endurance training.

The introduction to OSA and the role of physiotherapy shows the information about OSA and the role of physiotherapy in mitigating the severity of the disease.

The upper airway and respiratory muscle exercise part includes the list of exercises in this part (Figure 2). The page contains 3 main sections; the first is the review, and users can view the videos to familiarize themselves with the instructions before starting the official training. Here, users can actively select the exercises they want to see in the list of exercises. The second is the list of the exercises, users can click on the exercises they want to practice, but encourage users not to practice randomly, but should practice in numbered order to ensure they complete the whole program. The third section is the actual exercise program. There is a "Start training" button: when the button is clicked, the program will start from the 1st exercise on the list, followed by the rest of the exercise program. There is also a schedule function to help users remember the exercise time to achieve optimal training efficiency (Figure 3). In each exercise, there will be a video tutorial and text description to remind the user how to perform that exercise, users can play or stop the video tutorial at any time (Figure 4). When the user pressed the start (►) button, the application will play the video tutorials of each exercise by order of appearance. After finishing an exercise, there will be a 10–30 s break before the next exercise starts. When the user completes the whole set, a congratulations notice will pop up to congratulate the user (Figure 5).

The user interface for the general endurance exercise section is identical to the upper airway and respiratory muscle exercise section.

4. Discussion

The home-based rehabilitation program is becoming an essential part of many rehabilitation programs (17). It is even more so during the COVID-19 pandemic since for many places visiting the hospital for rehabilitation purposes may be considered an unnecessary risk (23). However, the nature of home-based rehabilitation dictates that the patient performs rehabilitation exercises without the supervision of a professional physical therapist or other medical professionals. Thus, the performance quality often relies solely on the patient's memory or the assisting family/caregiver, which is not an optimal approach for any treatment program. The use of smartphone applications for home-based rehabilitation programs has been a popular topic in the clinical community. Several studies have investigated the effect of smartphone applications on Parkinsonism, fall prevention, and exercise for the elderly (26–29). However, to the best of our

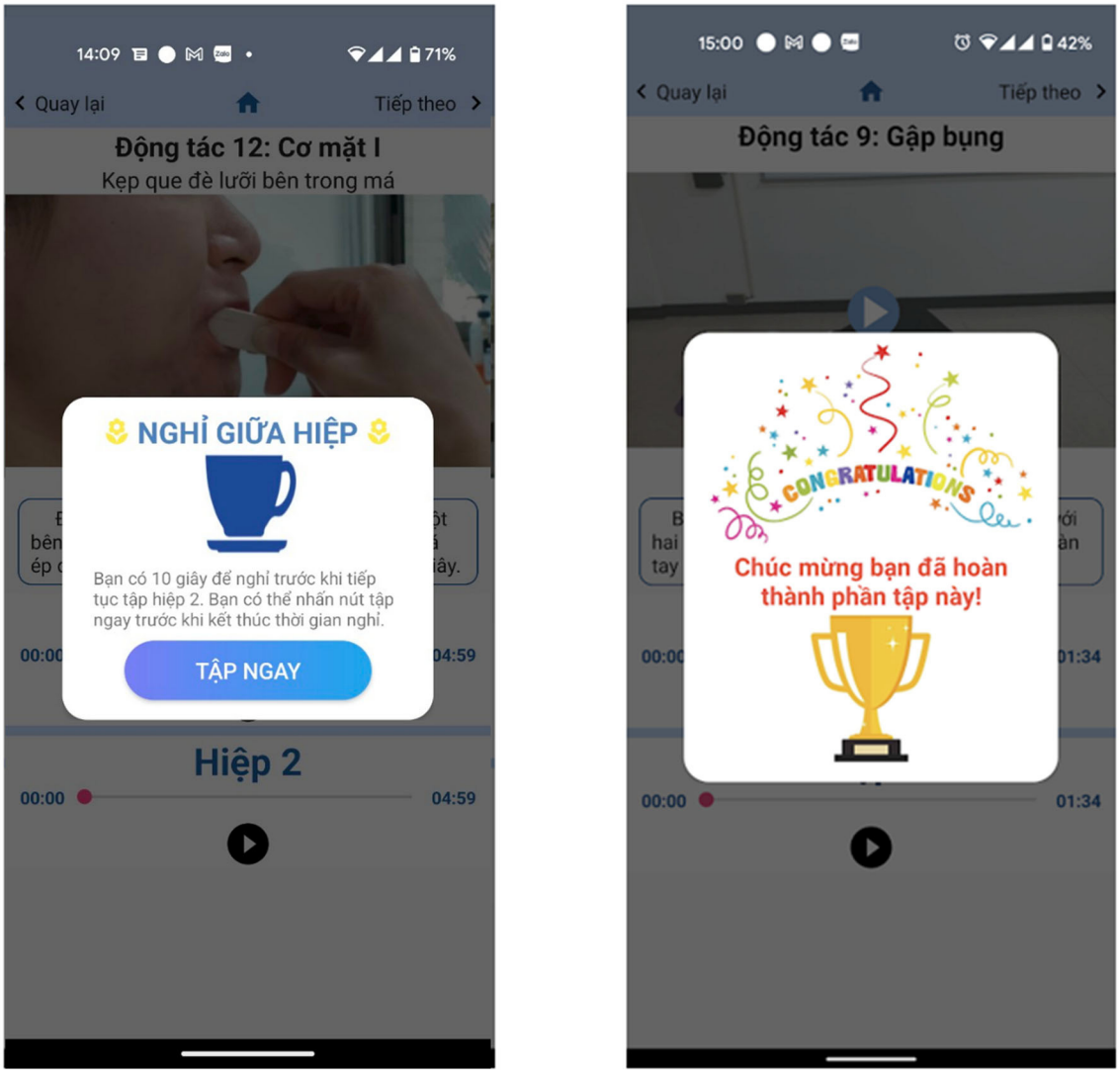

FIGURE 5
Screenshot of a break after set 1 and congratulations after finishing each part.

knowledge, there had not been a program, device, or application designed to assist patients with OSA in performing rehabilitation programs at home. Compared to rehabilitation programs for Parkinson's disease or fall prevention, which consist mostly of gross motor skills, the rehabilitation program for OSA requires a level of dexterity (15, 27, 28). Thus, it is even more critical that the patients with OSA can correctly perform the rehabilitation program at home to improve their condition. Our smartphone application enables the patients to review the step-by-step instruction of the rehabilitation program anytime, anywhere, thus improving the effectiveness of the habilitation program.

This application is designed for obstructive sleep apnea patients, at all levels of this syndrome, especially for those who cannot afford or tolerate CPAP therapy, or it can be an adjunct therapy to CPAP. According to the American Academy of Sleep Medicine Scoring Manual of Polysomnography, older children (from 13 years old) can be used for OSA diagnosis criteria as adults, so they can also practice these exercises (30). As for the technical aspect, some elderly may have difficulty using a smartphone, but they can also use the application with the help of their caregivers. In short, our design and exercises can be suitable for patients from 13 years old.

There are some applications for sleep apnea to practice upper airway muscle strength, such as Airway Gym and SnoreGym. However, these applications do not include general endurance exercises and there are no real-person videos like our design. In our application, the instructions are described in both video and text, once the patients are used to it, they can simply look at the exercise name and text instructions. Another advantage of our design is the narration in each set automatically runs, eliminating the need for patients to look at their phones constantly.

Although the application is a training aid, there are also some notices: self-discipline to complete exercises according to instructions, practice regularly according to the protocol, record how to practice correctly, and contact a doctor when needed support. Currently, our app can partially support patient

self-discipline and frequency through scheduling. The main limitation of the application is that it does not track the patient's movements, so the effect may be less than the direct exercises with the instructor. To achieve this tracking goal, we have the idea of using a phone camera when the patient is exercising, along with trained artificial intelligence to check the movement. However, this requires a large budget and time, so the research team has yet to be able to do it. In addition, the application design does not have a sleep tracking section (snoring and sleep-wake time), we will gradually develop it for the following versions. These limitations are challenges for telemedicine in general and smartphone apps in particular. In addition to the limitations mentioned above, our application also has the disadvantage that the design is not competitive, if it is designed as a game, the patients will be more motivated to exercise. These features will be studied in the future.

5. Conclusion

Our group plans to conduct a small-scale deployment and user study to investigate whether the application can effectively assist patients with OSA in performing their rehabilitation program at home. In addition, we also plan to conduct user interviews to understand what other functions the users would like to have in the application to further assist them in performing the rehabilitation program. Finally, we aim to achieve a large-scale randomized-controlled trial to investigate whether our application can benefit patients with OSA.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Institutional Review Board of the University of Medicine and Pharmacy at Ho Chi Minh City (UMP), Vietnam. Approval number: IRB-VN01002/IORG0008603/FWA00023448. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KB-D, C-HH, G-CZ, and SD-Q conceived the research idea and contributed to the final manuscript. KB-D, TN-B, and DT-T practiced the original PT exercises to design app flow, adjusted the commands and break time to suit the app version, and discussed ideas with the coding and design team. NT and QV-T-T advised on the protocol, the app, and OSA syndrome. DT-T discussed with the NCKU team about the original PT exercises and translated the exercises into Vietnamese. HN-T discussed ideas with the coding and design team and edited the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1124059/full#supplementary-material

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Effectiveness of internet-based CBT-I for the treatment of chronic subthreshold to moderate insomnia

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Study objectives: To study the effectiveness of the first internet-based cognitive behavioral therapy for insomnia (CBT-i) in Thailand, using the Nitra application, for chronic subthreshold to moderate insomnia treatment.

Methods: An interventional study without a control group was conducted between January and June 2022. Participants were adults aged 18 years old and older with subthreshold to moderate severity of chronic insomnia (insomnia severity index (ISI) of 8–21) and had mean sleep efficiency <85% from baseline sleep diaries. Baseline sleep characteristics were obtained from questionnaires and sleep diaries from the Nitra application for 2 weeks. Eligible participants continued using the Nitra application for 4 weeks during the intervention period. Interventions including sleep restriction, stimulus control, cognitive restructuring, relaxation techniques, and sleep hygiene education were implemented *via* the pre-programmed Nitra application. Post-intervention sleep characteristics were also obtained from questionnaires and sleep diaries from the Nitra application for another 1week.

Results: A total of 40 participants completed the study. All participants had a baseline sleep efficiency of less than 85% with the majority of the participants having a sleep-onset insomnia problem (98%). For the primary outcome, sleep efficiency was significantly improved after using the Nitra application ($p<0.001$). Self-reported total sleep time, sleep onset latency, wake after sleep onset, early morning awakening, ISI, Pittsburgh Sleep Quality Index (PSQI), and average subjective sleep quality were also significantly improved ($p<0.001$ for all parameters except $p=0.017$ for total sleep time and $p=0.018$ for wake after sleep onset). Participants who had a low baseline ISI and went to bed and woke up within 30 minutes of a designated bedtime and wake-up time recommended by the Nitra application for ≥70% of all nights demonstrated an increased chance of achieving normal sleep efficiency after using the Nitra application.

Conclusion: This first internet-based CBT-i in Thailand, using the Nitra application, effectively improved sleep efficiency and other sleep parameters in chronic subthreshold to moderate insomnia.

KEYWORDS

chronic insomnia, cognitive-behavioral therapy for insomnia, internet-based CBT-I, chronic subthreshold to moderate insomnia, sleep diary

1. Introduction

Insomnia is a common problem among the Thai population. The study by Sukying C in Thailand found that nearly half of the elderly population, who were aged more than 60 years old, had insomnia problems (1). Insomnia can impair the daytime function of the patients and cause a high economic burden related to direct costs (consultation and treatment of insomnia) and indirect costs (reduced productivity) (2). Benzodiazepines, as hypnotic medications, are the most commonly prescribed drug to patients with insomnia (3). However, there is evidence concerning the long-term use of these medications of the risk of dependence and tolerance over time and adverse effects such as daytime drowsiness, motor vehicle accidents, falling, and increased risk of developing dementia (4). Currently, the recommended standard treatment for chronic insomnia is cognitive behavioral therapy for insomnia (CBT-i) (5). This treatment is a multimodal intervention that includes sleep restriction, stimulus control, cognitive restructuring, relaxation techniques, and sleep hygiene education (6). Many studies have shown that CBT-i significantly improved patient's insomnia, and this effect was sustained in the long term, without adverse effects (7–9). However, due to the few available CBT-i providers, the frequency and long duration of each visit, and the requirement of hospital visits, access to CBT-i for many patients is limited.

However, with the generalized accessibility of internet technology, CBT-i can be delivered to many patients *via* the internet. Many studies showed that internet-based CBT-i could improve patient's insomnia and the effect was sustained in the long term like traditional CBT-i (10–13). However, some studies showed that internet-based CBT-i may not be as effective as traditional face-to-face CBT-I but it is still better than a placebo (14). Given the advantage of internet-based CBT-i in terms of more availability, more accessibility, and relatively lower costs, implementation of this treatment modality for insomnia seems to be appropriate. However, there is no currently available published literature examining the use of both face-to-face and internet-based CBT-i in Thailand. This study aims to evaluate the effectiveness of the first internet-based CBT-i in Thailand using the innovative Nitra application for the treatment of insomnia.

2. Materials and methods

2.1. Study design

This study was conducted as an interventional study without a control group to determine the effectiveness of internet-based CBT-i using the Nitra application for insomnia treatment in the Thai population.

Abbreviations: ISI, Insomnia severity index; ESS, Epworth Sleepiness Scale; MEQ, Morningness-Eveningness questionnaire; PSQI, Pittsburgh Sleep Quality Index; DBAS, Dysfunctional Beliefs and Attitudes about Sleep.

2.2. Participants

Recruitment of participants was conducted between January 2022 and June 2022. A poster with information about the study was advertised to the community *via* the official online website and the Facebook page of the Excellence Center for Sleep Disorders, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, and by a local poster published in the hospital. A total of 249 individuals with insomnia showed interest in participating in the study and applied *via* a Google Form linked to the QR code shown in the advertised poster. Telephone interviews, multiple questionnaires, and sleep diaries collected *via* the Nitra application were used to screen the potential research subjects using the inclusion and exclusion criteria. The inclusion criteria for participants included being at least 18 years old, having a clinical diagnosis of chronic insomnia disorders based on International Classification of Sleep Disorders, Version 3 (ICSD-3) criteria, with subthreshold to moderate severity of insomnia problem (insomnia severity index (ISI) of 8–21) and were able to access the Nitra application *via* a web browser on a smartphone, tablet, or computer. Since this application was the first internet-based CBT-i study in Thailand, severe insomnia patients, who would benefit from standard face-to-face CBT-i treatment, were not included in our study. The exclusion criteria included a history or high risk of other sleep disorders (obstructive sleep apnea, restless legs syndrome, or narcolepsy) or psychiatric disorders (bipolar disorder, major depressive disorder, anxiety disorder, or post-traumatic stress disorder), evaluated by standard questionnaires, namely STOP-Bang (15), IRLSSG (International Restless Legs Syndrome Study Group) questionnaire (16), ESS (Epworth Sleepiness Scale) (17), GAD-7 (Generalized anxiety disorder-7) (18), PHQ-9 (Patient Health Questionnaire-9) (19), and PTSD-5 (Posttraumatic stress disorder-5) (20). The participants would be considered high risk for obstructive sleep apnea, restless legs syndrome, narcolepsy, major depressive disorder, anxiety disorder, or post-traumatic stress disorder if they had STOP-Bang $\geq$5, IRLSSG = 4, ESS > 10 with at least 1 symptom of narcolepsy (sleep paralysis, hypnagogic or hypnopompic hallucination, or cataplexy), PHQ-9 $\geq$ 10, GAD-7 $\geq$ 10, or PTSD-5 $\geq$ 4, respectively. The participants who had recorded a mean sleep efficiency $\geq$85% in sleep diaries for 2 weeks were excluded. Information on each participant was collected by multiple questionnaires and sleep diaries recorded through the Nitra application. This information included baseline characteristics (age, sex, marital status, educational level, household salary, hypnotic medication use, caffeine use, alcohol use, and smoking) and sleep characteristics (circadian type by morningness-eveningness questionnaire (MEQ), ISI, Dysfunctional Beliefs and Attitudes about Sleep (DBAS), sleep quality by Pittsburgh Sleep Quality Index (PSQI), and sleep parameters by sleep diary record). All the participants who met the eligible criteria continued using the Nitra application for another 5 weeks (4 weeks of intervention period using the Nitra application and 1 week of post-intervention

evaluation). Finally, a total of 40 participants were enrolled in the study.

The Nitra application was developed by the team at the Excellence Center for Sleep Disorders, which was led by the authors of this study. The Nitra application is the first fully automated internet-based CBT-i developed in Thailand. During the 4-week intervention period, each participant had to input the data for the sleep diaries in the application every day and was encouraged to take part in the sleep education provided in the application. The Nitra application provided multimodal techniques to each participant including sleep restriction, stimulus control, cognitive restructuring, relaxation technique, and sleep hygiene education. For sleep restriction, the Nitra application was pre-programmed to provide a designated bedtime and wake-up time for each week based on the data of average sleep efficiency, average total sleep time, bedtimes, and wake-up times recorded during the previous week by each participant. A preferable wake-up time was also selected by the participants. Information about stimulus control, cognitive restructuring, relaxation techniques, and sleep hygiene education was provided to each participant through short articles, some with video clips embedded, in the Nitra application. Access to the articles by each participant was also recorded by the application when the participant manually clicked the button at the end of the article to confirm the finish of the reading. Good compliance with the sleep restriction technique was defined as the participant's bedtime and the wake-up time being within 30 minutes of the designated bedtime and wake-up time recommended by Nitra application for ≥70% of all nights. The cut point of 70% was used because this value implied that compliance was equal to 5 out of 7 days of a week. Good adherence to sleep education was defined as reading ≥50% of all articles provided by the application.

The sleep characteristics of each participant were evaluated again after completing the 4-week intervention period using the Nitra application. This information included ISI, sleep quality by PSQI, and sleep parameters recorded in the sleep diary for 1 week in the Nitra application.

2.3. Primary and secondary outcomes

The primary outcome was the change in sleep efficiency after using the Nitra application. The secondary outcomes included the change of other sleep parameters (total sleep time, sleep onset latency, wake after sleep onset, early morning awakening, time in bed, ISI, ESS, PSQI, and subjective sleep quality) after using the Nitra application, the percentage of participants achieving the normal value for each of the sleep parameters [sleep efficiency ≥85% (21), total sleep time ≥ 7 hours (22), sleep onset latency ≤30 minutes, wake after sleep onset ≤30 minutes, early morning awakening ≤30 minutes (21), ISI < 8 (23), and PSQI <6 (24)] after using the Nitra application, and factors associated with the improvement in sleep efficiency or achievement of normal sleep efficiency after using the Nitra application.

2.4. Statistical analysis

A sample size calculation was conducted using the data from the previous study by Zachariae R (12). The predicted sample size of 40 participants would provide a two-sided alpha level of 0.05 and a 90% power to detect a mean difference of 0.58 effect size of sleep efficiency change comparing between before and after using the Nitra application. This estimation assumed an approximately 20% loss to follow-up. The statistical analysis was as follows. For continuous variables, the data were reported as mean and standard deviation (normal distribution data), and median and interquartile range (non-normal distribution data). A paired *t*-test and Wilcoxon signed-rank test were used to compare dependent variables for normal distribution and non-normal distribution data, respectively. To compare independent variables, an unpaired *t*-test and Wilcoxon rank-sum test were used for parametric and non-parametric data, respectively. For categorical variables, the data were reported as counts and percentages. Comparison between dependent variables was done using McNemar's test and comparison between independent variables was done using a chi-square test or Fisher's exact test. A linear regression model was used to evaluate factors associated with sleep efficiency change after using the Nitra application and logistic regression models were used to evaluate factors associated with achieving normal sleep efficiency after using the Nitra application. Missing data was imputed using the data from the days before and after. Statistical analysis was performed using SPSS version 22. This study was approved by the ethics committee and registered at www.clinicaltrials.in.th (#TCTR20210901001). This research was financially supported by the Ratchadaphiseksomphot Endowment Fund of Chulalongkorn University.

3. Results

A total of 249 participants with insomnia showed interest in the study and applied *via* a Google Forms submission. Nine participants were unable to be contacted by telephone call and were excluded. Furthermore, 70 participants were excluded by telephone interviewing due to the following reasons: age < 18 years old, frequency of insomnia symptoms was less than 3 times/week, insomnia symptoms lasted less than 3 months, ISI was <8 or > 21, and history of comorbid sleep or psychiatric disorders. The remaining 170 participants were asked to register for the Nitra application and answer the screening questionnaires and record sleep diaries for 2 weeks. During this step, 125 participants were excluded: 25 participants did not register for the Nitra application, four participants registered for the Nitra application but did not answer the screening questionnaires, 88 participants met the exclusion criteria from the screening questionnaire, and eight participants had a mean sleep efficiency recorded during the first 2 weeks of ≥85%. A total of 45 participants were enrolled in this study with five participants requested to stop using the application during the study period. The remaining 40 participants completed the study.

From the total of 40 participants, the average age was 45 years old and most participants were female (77.5%) with a high educational level (90% finished a bachelor's degree or higher). From the MEQ test, the intermediate type was the most common (75%), followed by the evening type (9%), and only one participant was a morning type. More than half of the participants had a history of caffeine use (62.5%) and nearly all the participants did not use alcohol or smoke (92.5 and 97.5%, respectively). Only five participants currently used sedative medications for their insomnia problem. The average DBAS score was

99.6 from the maximum score of 160, which represented a trend of false belief and attitude about sleep (Table 1).

From sleep questionnaire data, the average ISI was 14.57, which was between the cut-off point of subthreshold and moderate severity. The average PSQI score was 11.32, which represented the poor sleep quality of the participants. From the sleep diary data, the baseline average sleep efficiency of participants was approximately 72% and total sleep time was approximately 6 hours. Sleep onset latency was the most prevalent problem (presented in 98% of the participants) and the most prolonged parameter when compared to the normal value (average sleep onset latency was 68 minutes). Early morning awakening was less prevalent (presented in 55% of the participants) and borderline prolonged when compared to the normal value (average early morning awakening duration was 34 minutes). Wake after sleep onset was present in only 15% of participants and the average duration of wake after sleep onset was still in the normal value (average wake after sleep onset duration was 18 minutes) (Tables 2, 3).

During the 4-week intervention period, 40% of the participants went to bed within 30 minutes of the designated bedtime recommended by the Nitra application for ≥70% of all nights and 45% of the participants got up within 30 minutes of the designated wake-up time recommended by the Nitra application for ≥70% of all nights. In total, 58% of the participants read ≥50% of all the articles provided by the application.

There was a significant improvement in many parameters from the sleep diary when comparing before and after using the Nitra application. These included sleep efficiency [71.94 ± 11.20 vs. 86.53 ± 7.02 (mean difference 14.58; 95% CI 11.35–17.80, $p < 0.001$)], total sleep time [6.07 ± 0.97 vs. 6.39 ± 0.91 (mean difference 0.31; 95% CI 0.05–0.57, $p = 0.017$)], sleep onset latency [68.21 (44.46, 90) vs. 28.93 (18.43, 41.71) (mean difference − 45.59; 95% CI -60.14- -31.03, $p < 0.001$)], wake after sleep onset [17.60 (8.35, 26.6) vs. 8.28 (4.29, 17.35) (mean difference − 9.73; 95% CI -17.72- -1.74, $p = 0.018$)], and early morning awakening [33.75 (19.82, 58.93) vs. 9.64 (5, 19.64) (mean difference − 31.81; 95% CI -20.32- -43.31, $p < 0.001$)]. Time in bed was also significantly decreased [8.5 ± 0.99 vs. 7.4 ± 0.82 (mean difference − 1.09; 95% CI -1.47- -0.72, $p < 0.001$)] (Table 2).

For the other sleep parameters from the sleep questionnaire, there was also a significant improvement in ISI [(14.57 ± 3.49 vs. 8.7 ± 4.14 (mean difference − 5.87; 95% CI -7.37- -4.37, $p < 0.001$)], PSQI [(11.32 ± 2.86 vs. 6.55 ± 2.76) (mean difference − 4.77; 95% CI -5.81- -3.73, $p < 0.001$)], and average subjective sleep quality [(2.92 ± 0.45 vs. 3.54 ± 0.72) (mean difference 0.57; 95% CI -0.35-0.79, $p < 0.001$)] after using the Nitra application (Table 2).

When comparing the proportion of participants who had a normal value of each sleep parameter before and after using the Nitra application, there was a significant increase in the proportion of the participants who had normal sleep efficiency (≥ 85%) (0% vs. 62.5%, $p < 0.001$), total sleep time (≥ 7 hours) (17.5% vs. 32.5%, $p < 0.001$), sleep onset latency (≤ 30 minutes) (5% vs. 55%, $p < 0.001$), wake after sleep onset (≤ 30 minutes) (85% vs. 90%, $p < 0.001$), and early morning awakening (≤ 30 minutes) (45% vs. 97.5%, $p < 0.001$). The proportion of the participants who had normal values of ISI (<8) and PSQI (<6) also increased significantly (0% vs. 35%, $p < 0.001$ and 0% vs. 40%, $p < 0.001$, respectively) (Table 3).

When the evaluation was made to identify the factors associated with the change in sleep efficiency after using the Nitra application, no factors were shown to be significantly associated with the change in sleep efficiency (Table 4).

However, when the evaluation was made to identify the factors associated with achieving normal sleep efficiency after using the Nitra application, participants who had a low baseline ISI and went to bed and woke up within 30 minutes of the designated bedtime and wake-up time recommended by Nitra application for ≥70% of all nights demonstrated an increased chance of achieving normal sleep efficiency after using the Nitra

TABLE 1 Baseline characteristics.

Parameter	Participants (n =40)	
	Mean±S.D.	n (%)
Age	45.75 ± 12.74	–
Sex		
Male	–	9 (22.5)
Female	–	31 (77.5)
Marital status		
Single	–	26 (65)
Married	–	12 (30)
Married, separated	–	2 (5)
Education		
Secondary school/ Vocational certificate	-	4 (10.00)
Bachelor's degree	–	21 (52.5)
Higher than a bachelor's degree	–	15 (37.5)
Household salary		
< 20,000 THB/month	–	6 (15)
20,000–49,999 THB/month	–	18 (45)
50,000–100,000 THB/month	–	13 (32.5)
> 100,000 THB/month	–	3 (7.5)
MEQ Group		
Morning type	–	1 (2.5)
Intermediate type	–	30 (75)
Evening type	–	9 (22.5)
Caffeine		
Not use	–	15 (37.5)
Use	–	25 (62.5)
Alcohol		
Not use	–	37 (92.5)
Use	–	3 (7.5)
Smoking		
Not use	–	39 (97.5)
Use	–	1 (2.5)
Sedative drug		
Not use	–	35 (87.5)
Use	–	5 (12.5)
DBAS	99.6 ± 22.13	–

MEQ, Morningness-Eveningness Questionnaire; DBAS, Dysfunctional Beliefs and Attitudes about Sleep

TABLE 2 Pre and post-sleep parameters.

Parameter	Pre [mean±S.D. or median (IQR)]	Post [mean±S.D. or median (IQR)]	Different [mean (95% CI)]	*p* value
Sleep efficiency (%)	71.94 ± 11.20	86.53 ± 7.02	14.58 (11.35, 17.80)	<0.001*
Total sleep time (hours)	6.07 ± 0.97	6.39 ± 0.91	0.31 (0.05, 0.57)	0.017*
Sleep onset latency (minutes)	68.21 (44.46, 90)	28.93 (18.43, 41.71)	−45.59 (−60.14, −31.03)	<0.001*
Wake after sleep onset (minutes)	17.60 (8.35, 26.6)	8.28 (4.29, 17.35)	−9.73 (−17.72, −1.74)	0.018*
Early morning awakening (minutes)	33.75 (19.82, 58.93)	9.64 (5, 19.64)	−31.81 (−20.32, −43.31)	<0.001*
Time in bed (hours)	8.5 ± 0.99	7.4 ± 0.82	−1.09 (−1.47, −0.72)	<0.001*
ISI	14.57 ± 3.49	8.7 ± 4.14	−5.87 (−7.37, −4.37)	<0.001*
ESS	6.5 (4, 9)	4 (2.5, 6)	−2.02 (−3.29, −0.75)	0.002*
PSQI	11.32 ± 2.86	6.55 ± 2.76	−4.77 (−5.81, −3.73)	<0.001*
Subjective sleep quality	2.92 ± 0.45	3.54 ± 0.72	0.57 (0.35, 0.79)	<0.001*

ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index. * = $p < 0.05$.

TABLE 3 Pre and post-proportion of the participants with normal values for each sleep parameter.

Parameter	Pre [*n* (%)]	Post [*n* (%)]	*p* value
Sleep efficiency (%)			
< 85%	40 (100)	15 (37.5)	<0.001*
>/= 85%	0 (0)	25 (62.5)	
Total sleep time (hours)			
< 7	33 (82.5)	27 (67.5)	<0.001*
>/= 7	7 (17.5)	13 (32.5)	
Sleep onset latency (minutes)			
> 30	38 (98)	18 (45)	<0.001*
</= 30	2 (5)	22 (55)	
Wake after sleep onset (minutes)			
> 30	6 (15)	4 (10)	<0.001*
</= 30	34 (85)	36 (90)	
Early morning awakening (minutes)			
> 30	22 (55)	1 (2.5)	<0.001*
</= 30	18 (45)	39 (97.5)	
ISI			
>/= 8	40 (100)	26 (65)	<0.001*
< 8	0 (0)	14 (35)	
ESS			
> 10	5 (12.5)	3 (7.5)	<0.001*
</= 10	35 (87.5)	37 (92.5)	
PSQI			
>/= 6	40 (100)	24 (60)	<0.001*
< 6	0 (0)	16 (40)	

ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index. * = $p < 0.05$.

application (Table 5). The odds ratio of each factor was 0.78 (95% CI 0.63–0.97), 4.33 (95% CI 0.97–19.20), and 1.34 (95% CI 1.34–26.80), respectively (Table 6).

4. Discussion

This is the first study that has evaluated the effectiveness of the first internet-based CBT-i in Thailand (Nitra application). The results from our study demonstrated that the Nitra application effectively improved participants' insomnia in many aspects. For the primary outcome, sleep efficiency was significantly increased by approximately 15% after completing 4 weeks of internet-based CBT-i sessions using the Nitra application. This result approximated the result from a previous study conducted by Collin A Espie in 2012 (10), which showed that 6 weekly sessions of online CBT-i were able to significantly increase sleep efficiency by approximately 20% compared to the baseline before attending online CBT-i. The difference in sleep efficiency improvement between our study and the aforementioned study may be related to the duration of CBT-i therapy, in which a longer duration may result in a greater improvement in sleep efficiency. However, approximately two-thirds of the participants achieved normal sleep efficiency (sleep efficiency ≥85%) after using the Nitra application.

Average total sleep time after study completion increased by approximately 19 minutes from baseline. This borderline increase in total sleep time was likely due to the short CBT-i intervention period of our study (4 weeks). The protocol of sleep restriction in our study limited the extension of sleep time to 15 minutes per week if the sleep efficiency from the previous week was >85%. This protocol resulted in a maximum extension of sleep duration of 45 minutes after study completion. When compared to the previous study of Collin A Espie (10), which showed an increase of total sleep time of 39 minutes after 6 weekly sessions of online CBT-i, extending the duration of the intervention period would likely result in a further increase in total sleep time.

Sleep onset latency, wake after sleep onset, and early morning awakening duration were significantly improved after completing the study. However, nearly half of the participants (45%) still had a sleep onset latency of longer than 30 minutes even though this was significantly decreased from the baseline (98%). For wake after sleep onset and early morning awakening, only a small number of participants (10 and 2%, respectively) still experienced these sleep parameters longer than 30 minutes. However, in our study, sleep onset latency was calculated by the duration between the time when the

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TABLE 4 Evaluation of the factors associated with sleep efficiency change after using the Nitra application.

Factor	Delta Post - Pre S.E	*p* value
Age		0.466
Sex		
Male [median (IQR)]	12 (10, 25.07)	0.570
Female [median (IQR)]	13.07 (7.07, 20.93)	
Marital status		
Single [median (IQR)]	12.57 (7.07, 20.93)	0.624
Married [median (IQR)]	13.68 (9.36, 22.54)	
Married, separated [median (IQR)]	9.89 (8.21, 11.57)	
Education		
Secondary school/ Vocational certificate [median (IQR)]	20.965 (6.57, 36.86)	0.362
Bachelor's degree [median (IQR)]	13.22 (10, 21.79)	
Higher than bachelor's degree (median (IQR)]	11.79 (4.85, 14.78)	
Household salary		
< 20,000 THB/month [median (IQR)]	15.745 (11.79, 26.28)	0.717
20,000–49,999 THB/month [median (IQR)]	13.18 (4.93, 21.79)	
50,000–100,000 THB/month [median (IQR)]	12 (9.07, 15.36)	
> 100,000 THB/month [median (IQR)]	13.57 (8.28, 25.07)	
MEQ Group		
Morning type [median (IQR)]	13.22 (13.22, 13.22)	0.567
Intermediate type [median (IQR)]	11.925 (6.07, 21.79)	
Evening type [median (IQR)]	13.14 (9.36, 20.93)	
Baseline ISI		0.360
Baseline ESS		0.124
DBAS		0.763
Baseline PSQI		0.087
Caffeine		
Not use [median (IQR)]	10 (6.07, 20.93)	0.342
Use (median (IQR)]	13.57 (9.36, 21.79)	
Alcohol		
Not use [median (IQR)]	12.13 (8.21, 21.79)	0.857
Use [median (IQR)]	13.07 (9.07, 14.29)	
Smoking		
Not use [median (IQR)]	12.13 (8.21, 20.93)	0.152
Use [median (IQR)]	31.43 (31.43, 31.43)	
Sedative drug		
Not use [median (IQR)]	12.13 (8.21, 21.79)	0.838
Use [median (IQR)]	13.57 (9.36, 18.86)	
Article read		
Read <50% of all articles [median (IQR)]	10 (4.93, 14.29)	0.250
Read >/= 50% of all articles [median (IQR)]	13.14 (9.36, 23.29)	
Bedtime within 30 minutes of the designated time		
< 70% of all bedtime [median (IQR)]	11.89 (5.5, 20.28)	0.171
>/= 70% of all bedtime [median (IQR)]	13.96 (10.46, 23.53)	
Wake-up time within 30 minutes of the designated time		
< 70% of all bedtime [median (IQR)]	12.67 (8.21, 23.29)	0.989
>/= 70% of all bedtime [median (IQR)]	12.46 (8.28, 18.86)	

MEQ, Morningness-Eveningness Questionnaire; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; DBAS, Dysfunctional Beliefs and Attitudes about Sleep; PSQI, Pittsburgh Sleep Quality Index.

participants went to bed and the estimated time when the participants fell asleep, which may be overestimated due to some proportion of the time may not be intended to sleep (e.g., using a cellphone or watching TV during being on the bed). This limitation may have overestimated the baseline severity and underestimated the improvement of sleep onset insomnia in our study.

ISI, PSQI, and average subjective sleep quality showed significant improvements. However, only a minority of the participants (25%) achieved a normal ISI (< 8) after using the Nitra application. For PSQI, nearly half of the participants (40%) achieved a normal PSQI (< 6) after completing the intervention period.

When evaluated for the factors associated with achieving normal sleep efficiency after using the Nitra application, lower baseline ISI was associated with a higher chance of achieving normal sleep efficiency after completing the intervention. This finding was not surprising because a lower baseline ISI represented a lower insomnia severity, which would have a higher chance of being resolved after attending CBT-i. This finding also supported that the Nitra application could also be applicable to a non-insomnia population who has the tendency to develop insomnia. Compliance with the designated bedtime and wake-up time recommended by the Nitra application (which was defined by a participant's actual bedtime and wake-up time being within 30 minutes of the designated bedtime and wake-up time by Nitra application for ≥70% of all nights) was also a predictor for a higher chance of achieving normal sleep efficiency (≥ 85%) after using the Nitra application. These findings supported the current evidence that the sleep restriction technique is one of the most effective techniques of CBT-i (25).

Nevertheless, there were some limitations in our study. First, the short intervention period (4 weeks) may have limited improvement of both the objective and subjective parameters of insomnia in our study. We hypothesize that extending the period of using the Nitra application may result in a further increase in sleep efficiency, total sleep time, and the proportion of participants resolving their insomnia. Second, sleep onset latency and early morning awakening in our study may be overestimated. A more detailed version of a sleep diary that can record the starting time in bed, the time intended to sleep, the time intended to wake up, and the wake-up time may reflect more accurate sleep onset latency and early morning awakening. Third, the number of articles read by each participant was recorded only when the participants manually clicked the button at the end of the article

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TABLE 5 Evaluation of the factors associated with achieving normal sleep efficiency after using the Nitra application.

Factor	Post S.E. < 85%	Post S.E. >/= 85%	*p* value
Age (mean ± S.D.)	48.06 ± 12.98	44.36 ± 12.65	0.380
Sex			
Male [*n* (%)]	4 (26.67)	5 (20.00)	0.705
Female [*n* (%)]	11 (73.33)	20 (80.00)	
Marital status			
Single [*n* (%)]	9 (60.00)	17 (68.00)	0.266
Married [*n* (%)]	4 (26.67)	8 (32.00)	
Married, separated [*n* (%)]	2 (13.33)	0 (0)	
Education			
Secondary school/ Vocational certificate [*n* (%)]	3 (20.00)	1 (4.00)	0.362
Bachelor's degree [*n* (%)]	7 (46.67)	14 (56.00)	
Higher than bachelor's degree [*n* (%)]	5 (33.33)	10 (40.00)	
Household salary			
< 20,000 THB/month [*n* (%)]	2 (13.33)	4 (16.00)	1.000
20,000–49,999 THB/ month [*n* (%)]	7 (46.67)	11 (44.00)	
50,000–100,000 THB/ month [*n* (%)]	5 (33.33)	8 (32.00)	
> 100,000 THB/month [*n* (%)]	1 (6.67)	2 (8.00)	
MEQ Group			
Morning type [*n* (%)]	1 (6.67)	0	0.054
Intermediate type [*n* (%)]	13 (86.67)	17 (68.00)	
Evening type [*n* (%)]	1 (6.67)	8 (32.00)	
Baseline ISI (mean ± S.D.)	16.2 ± 3.02	13.6 ± 3.43	0.020*
Baseline ESS (mean ± S.D.)	6 ± 3.94	7.4 ± 3.14	0.223
DBAS (mean ± S.D.)	98.53 ± 18.05	100.24 ± 24.59	0.816
Baseline PSQI (mean ± S.D.)	11.2 ± 3.12	11.4 ± 2.76	0.834
Caffeine			
Not use [*n* (%)]	7 (46.67)	8 (32.00)	0.354
Use [*n* (%)]	8 (53.33)	17 (68.00)	
Alcohol			
Not use [*n* (%)]	15 (100.00)	22 (88.00)	0.279
Use [*n* (%)]	0 (0)	3 (88.00)	
Smoking			
Not use [*n* (%)]	15 (100.00)	24 (96.00)	1.000
Use [*n* (%)]	0 (0)	1 (4.00)	
Sedative drug			
Not use [*n* (%)]	13 (86.67)	22 (88.00)	1.000
Use [*n* (%)]	2 (13.33)	3 (12.00)	
Article read			
Read <50% of all articles [*n* (%)]	7 (46.67)	10 (53.33)	0.680
Read >/= 50% of all articles [*n* (%)]	8 (53.33)	15 (60.00)	
Bedtime within 30 minutes of designated time			
< 70% of all bedtime [*n* (%)]	12 (80.00)	12 (48.00)	0.046*
>/= 70% of all bedtime [*n* (%)]	3 (20.00)	13 (52.00)	
Wake up time within 30 minutes of designated time			
< 70% of all bedtime [*n* (%)]	12 (80.00)	10 (40.00)	0.014*
>/= 70% of all bedtime [*n* (%)]	3 (20.00)	15 (60.00)	

MEQ, Morningness-Eveningness Questionnaire; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; DBAS, Dysfunctional Beliefs and Attitudes about Sleep; PSQI, Pittsburgh Sleep Quality Index. * = $p < 0.05$.

TABLE 6 The odds ratio of each factor associated with achieving normal sleep efficiency after using the Nitra application.

Factor	Odds ratio	95% CI	*p* value
Baseline ISI	0.78	0.63–0.97	0.028*
Bedtime within 30 minutes of the designated time			
< 70% of all bedtime [*n* (%)]	1		
>/= 70% of all bedtime [*n* (%)]	4.33	0.97–19.20	0.054
Wake-up time within 30 minutes of the designated time			
< 70% of all bedtime [*n* (%)]	1		0.019*
>/= 70% of all bedtime [*n* (%)]	6	1.34–26.80	

ISI, Insomnia Severity Index. * = $p < 0.05$.

to confirm they had finished reading. This may have caused an underestimation of the number of articles read by each participant. Automatic article reading tracking may result in more accurate information. Finally, the exclusion of participants who had normal sleep efficiency (≥ 85%) may limit the generalizability of our findings to people with insomnia by ICSD-3 criteria but failed to include self-reported sleep deficits. Less stringent inclusion and exclusion criteria for participants in the future study may make more generalizability of the intervention for patients with insomnia symptoms. In conclusion, the Nitra application effectively improved participants' sleep efficiency and other parameters in chronic subthreshold to moderate insomnia. Future study with a longer intervention period, automatic data tracking, and more detailed sleep diary

record is needed to further study the efficacy of the Nitra application.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board, Faculty of Medicine, Chulalongkorn University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WT, KT, DM, NC, and PS conceptualized, validated, and wrote the original draft of the manuscript. WT conducted the study. WT, DM, NC, and PS analyzed the data of the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Study of the obstructive sleep apnea syndrome in cerebral infarction patients

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Introduction: Obstructive Sleep Apnea Syndrome (OSAS) is the most common respiratory disorder during sleep. Many studies have shown an association between obstructive sleep apnea syndrome and stroke, and OSAS has not been adequately considered in Vietnam compared to the actual clinical dangers. This study aims to assess the prevalence and general characteristics of obstructive sleep apnea syndrome in patients with cerebral infarction and investigate the relationship between obstructive sleep apnea syndrome and the severity of cerebral infarction.

Methods: Descriptive cross-sectional study. We identified 56 participants from August 2018 to July 2019. Subacute infarcts were identified by neuroradiologists. For each participant, vascular risk factors, medications, clinical symptoms, and neurological examination were abstracted from the medical record. Patients were taken for history and clinical examination. The patients were divided into two groups according to their AHI (Apnea-Hypopnea Index) (<5 and ≥ 5).

Results: A total of 56 patients were registered for the study. The mean age is 67.70 $\pm$ 11.07. The proportion of men is 53.6%. AHI has a positive correlation with neck circumference ($r = 0.4$), BMI ($r = 0.38$), the Epworth Sleepiness Scale ($r = 0.61$), LDL cholesterol ($r = 0.38$), the Modified Rankin Scale ($r = 0.49$), NIHSS (National Institutes of Health Stroke Scale) ($r = 0.53$), and an inverse correlation with SpO_2 ($r = 0.61$).

Conclusion: Obstructive sleep apnea Syndrome is a factor in the prognosis of cerebral infarction as well as cardiovascular diseases such as hypertension. Thus, understanding the risk of stroke in people with sleep apnea is necessary and working with a doctor to diagnose and treat sleep apnea is important.

KEYWORDS

obstructive sleep apnea syndrome (OSAS), OSA, apnea-hypopnea index (AHI), stroke, respiratory polygraphy

Introduction

Obstructive sleep apnea (OSA) is a chronic sleep-related breathing disorder characterized by recurrent partial or complete cessation of airflow due to upper airway obstruction during sleep that results in sleep fragmentation, intermittent hypoxia, and hypercapnia leading to increased sympathetic nervous system activity (1). OSA has a prevalence reaching 8.5% of the adult population in Viet Nam considering all OSA severities (2). Night-to-night AHI variability does not have a definitive explanation but is reported in polysomnography measurements and should be considered in treatment decisions (3, 4).

Patients with OSA may exhibit loud and chronic snoring, gasping episodes during sleep, sleepiness, obesity, and increased neck circumference (5). OSA is associated with physical examination alterations and systemic complaints, including daytime fatigue and impaired concentration (6). OSA is also an independent risk factor for arterial hypertension, stroke, ischemic heart disease, cardiac arrhythmia, and heart failure (1).

Cerebral infarction tends to increase because the risk factors for the disease do not decrease such as a sedentary lifestyle, a high-fat diet such as fast food, high-sugar drinks, stress and high blood pressure, diabetes, and smoking become common (7).

Patients with ischemic stroke often develop sleep apnea and are common within the first 24 h. Disorderly breathing can be worse if the stroke happens while patients are asleep. OSA is the most common kind of sleep apnea that takes place after a stroke. OSA affects up to 70% of people with a stroke, compared to 30% of the overall population. A major aspect of medical care is the detection and treatment of OSA, as a treatment for OSA may enhance a person's recovery and decrease the risk of additional strokes. The relationship between stroke and OSA is bidirectional:

Kim et al. studied 80 patients with stroke and concluded that OSAS could cause dysfunction in patients with cerebrovascular accidents (8).

Ahn et al., when studying 293 patients with 159 men and 134 women with acute cerebral infarction, 63.1% (111 men, 74 women) had SAS, mainly OSAS with AHI >10 and at the same time concluded the relationship between SAS and the score of the National Institutes Of Health Stroke Scale (NIHSS: National Institutes Of Health Stroke Scale) and the adjusted Rankin Scale (mRankin: Modified Rankin Scale) high and worse long-term outcomes compared with the group without SAS (9).

Mattaliano et al. when studying 130 patients with acute cerebral infarction, the results showed that 61.9% had OSAS, most of which were men accounting for 67.1%. This study confirms the high prevalence of OSA in stroke patients and shows an association between OSA and target organ damage (10).

Researchers have identified OSA as an independent risk factor for stroke. This means that people with OSA are at higher risk of stroke, even if there are no other risk factors. There are several possible reasons for why people with OSA have a higher risk of stroke. Repeated collapses of the airway during sleep create negative air pressure within the chest, which may slow the flow of blood to the brain, thereby altering cerebral vascular abnormalities. OSA increases the risk of developing heart disease, hypertension, diabetes, and heart arrhythmias. These and other health consequences of OSA can increase the risk of stroke. These and other effects may be associated with an increased risk of stroke.

Many studies have shown an association between obstructive sleep apnea syndrome and hypertension, coronary artery disease, arrhythmia, and systolic heart failure (11, 12). Numerous studies have also mentioned the association between sleep apnea syndrome and stroke (13, 14). Based on this situation, we conducted a study that aims to achieve two objectives:

1. Evaluation of prevalence and general characteristics of obstructive sleep apnea syndrome in patients with cerebral infarction.
2. Investigate the relationship between obstructive sleep apnea syndrome and the severity of cerebral infarction.

Methods

Subjects

A total of 56 patients were diagnosed with subacute cerebral infarction and treated at the Cardiology Department of Hue University of Medicine and Pharmacy Hospital.

Obstructive sleep apnea Diagnostic Criteria were recommended by the American Academy of Sleep Medicine 2008 (AASM: American Academy of Sleep Medicine) (15). The patient suspected of OSAS must fulfill criterion A or B, plus criterion C. These are as follows:

A. Excessive daytime sleepiness that is not better explained by other factors.
B. Two or more of the following that are not better explained by other factors:

- Choking or gasping during sleep
- Recurrent awakenings from sleep
- Unrefreshing sleep
- Daytime fatigue
- Impaired concentration

C. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort–related arousals, as defined below.

Inclusion criteria

All subjects aged over 15 and fulfilling the criteria for a clinician-confirmed diagnosis of subacute cerebral infarction as defined by neuroradiologists were included in the study.

Exclusion criteria

- Patients with acute and severe diseases, chronic obstructive pulmonary disease or chronic respiratory failure, and cerebral diseases such as cerebral tumors, meningitis, and encephalitis.
- Patients who do not agree or cannot participate in the study.
- The patient is taking drugs that affect respiratory polygraph.

Methods

We identified 56 participants from August 2018 to July 2019. Subacute infarcts were determined by neuroradiologists. For each participant, vascular risk factors, medications, clinical symptoms, NIHSS, Epworth, and neurological examination were abstracted from the medical record. The study sample included 40 subacute cerebral infarction patients with OSA and 16 subacute cerebral

Abbreviations: OSAS, Obstructive Sleep Apnea Syndrome; AHI, Apnea-Hypopnea Index; NIHSS, National Institutes of Health Stroke Scale; AASM, American academy of sleep medicine; BMI, Body Mass Index.

infarction patients without OSA. Assess outcomes at 3 months after stroke with mRankin, face-to-face visit, or telephone.

Study design

It was a descriptive cross-sectional research method with follow-up.

Anthropometry

Patients were weighed using a calibrated scale to the nearest 0.1 kg, and height (to 0.1 cm) was measured with a stadiometer (Medisol, Vietnam). Body mass index (BMI) was classified by WHO in 1986.

Respiratory polygraphy

The respiratory polygraphy system used in the study is the Embletta GOLD. Embletta GOLD recorded nasal airflow, snoring using a nasal pressure cannula, blood oxygen saturation, heart rate by pulse oximetry, and respiratory effort using a thoracic piezoelectric chest belt.

The device will be provided to patients with an explanation of how to use it in advance, as well as precise instructions on the correct positioning of the equipment's sensors and monitoring. Patients will also conduct several tests to familiarize themselves with the instrument's operating instructions. When the device is returned the next day, raw data files will be uploaded to a computer and recorded automatically and manually by trained physicians from the Study Group. A respiratory polygraphy recording will be deemed valid if the recording duration is $\geq$5 h. Sections with artifacts or poor signals will be excluded from the analysis. If respiratory polygraphy is not valid, it will be repeated within the next 7 days.

OSA criteria

The diagnostic criteria for adult OSA as defined by the American Academy of Sleep Medicine (16).

Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort–related arousals, as defined below.

This report also proposed a grading of severity of OSAS based on the frequency of abnormal respiratory events during sleep: Mild: $\geq$5 but <15 events/hour of sleep; Moderate: 15–30 events/hour of sleep; Severe: More than 30 events/hour of sleep.

The definition and severity of subacute infarction

Classification of cerebral infarction by time (17):

- Acute cerebral infarction: from the first day of the 1st week after symptom onset.
- Subacute cerebral infarction: from the second week to 1 month.
- Chronic cerebral infarction: After 1 month.

The severity of cerebral infarction was based on NIHSS and mRankin. Stroke severity was categorized as follows: no stroke symptoms (0), minor stroke (1–4), moderate stroke (5–15), moderate to severe stroke (16–20), and severe stroke (21–42). In our study, the highest score was 14, thus, we divided it into two groups: 0–4 and 5–14 (18).

The original mRankin defined grade 1 as "No significant disability: able to carry out all usual duties," and defined grade 2 as "Slight disability: unable to carry out some of the previous activities." Patients with an mRs score $\leq$2 by definition are independent (19).

Data collection

All data on age, gender, height, weight, BMI, medical and family history, clinical characteristics, and respiratory polygraphy parameters (AHI, SpO_2, pulse, and frequency of snoring) of the study subjects were collected for statistical analyses.

Ethical approval

All procedures performed in studies involving human participants followed the institutional and/or national research committee's ethical standards and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Hue University of Medicine and Pharmacy Institutional Ethical Review Board. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

SPSS 22.0 software (IBM Corporation, Armonk, NY, USA) was used to analyze these collected data. Qualitative data are expressed as percentages or rates and compared with the Chi-squared test. Continuous variables were presented as mean $\pm$ standard deviation (SD) and compared with a *t*-test between 2 groups and a one-way analysis of variance among groups, followed by paired comparison with the least-significant difference test. A value of $p < 0$ 0.05 was considered statistically significant.

Results

General characteristics of study subjects

During the study period, 56 patients with subacute infarcts met the inclusion criteria and were enrolled in this study. The demographic characteristics (gender, age, neck circumference, waist circumference, and BMI) of the study population are shown in Table 1. There was no statistically significant difference between age and gender for both groups. The mean age is 67.70 $\pm$ 11.07. The proportion of men is 53.6% (Table 1).

The OSAS group was statistically higher in neck circumference and BMI (Body Mass Index) than the group without OSAS ($p < 0.05$).

Cardiovascular risk factors include smoking history, overweight and obesity, hypertension, and dyslipidemia. The results of this study noted that the prevalence of overweight and obesity was statistically higher in the group with OSAS ($p < 0.05$).

TABLE 1 Age group, gender, body measurements, and cardiovascular disease risk factors.

General characteristics ($n = 56$)		Non-OSAS		OSAS		Total		p
	n	%	n	%	n	%		
Gender	Male	7	12.5	23	41.1	30	53.6	>0.05
	Female	9	16.1	17	30.4	26	46.4	
Age	<50	1	1.8	1	1.8	2	3.6	>0.05
	50–69	9	16.1	24	42.9	33	58.9	
	≥70	6	10.7	15	26.8	21	37.5	
Body measurements	Neck circumference (cm)	36.19 ± 1.07		37.25 ± 1.92		36.95 ± 1.24		**<0.05**
	Waist circumference (cm)	84.25 ± 2.05		84.95 ± 1.87		84.75 ± 1.93		>0.05
	BMI (kg/m^2)	19.09 ± 2.37		21.56 ± 2.98		20.86 ± 3.02		**<0.05**
Smoking history		5	8.9	16	28.6	21		>0.05
Overweight and obesity		1	1.8	13	23.2	14		**<0.05**
Hypertension		13	23.2	38	67.9	51		>0.05
Dyslipidemia		9	16.1	30	53.6	39		>0.05

BMI, body mass index; OSAS, Obstructive Sleep Apnea Syndrome. The bold values mean statistically significant difference (with $p < 0.05$).

TABLE 2 The classification of OSA severity.

AHI (event/hour)	n	Ratio (%)
5 to <15	5	12.5
15–30	30	75.0
>30	5	12.5

AHI, apnea-hypopnea index.

TABLE 3 Index for the respiratory polygraph and characteristics of blood pressure.

Characteristics		Non-OSAS	OSAS	P
Average SpO_2 (%)	Median	95.8	90.0	**<0.05**
	Variation	95–97	85–95.2	
Lowest SpO_2 (%)	Median	93.5	83	**<0.05**
	Variation	88–95	79–92	
Measurement time (minutes)	$\bar{X} \pm SD$	500.1 ± 28.8	483.2 ± 35.7	>0.05
Systolic blood pressure (mmHg)	Median	150	150	>0.05
	Variation	110–180	120–260	
Diastolic blood pressure (mmHg)	Median	80	85	**<0.05**
	Variation	70–100	60–120	

The bold values mean statistically significant difference (with $p < 0.05$).

Clinical and laboratory features

Table 2 summarizes the severity of OSA based on AHI results measured from respiratory polygraphs. According to our research, the moderate OSA group accounted for the highest rate of 75%; the mild and severe OSA groups accounted for the same with 12.5% (Table 2).

The results table below shows the index for the respiratory polygraph and the characteristics of blood pressure which include average SpO_2, Lowest SpO_2, measurement time, systolic blood pressure, and diastolic blood pressure. The average and lowest SpO_2 were statistically smaller in the OSA group than in the non-OSA group ($p < 0.05$). We are interested in systolic blood pressure and diastolic blood pressure. In addition, we found that diastolic blood pressure in the OSAS group was statistically higher than in the non-OSAS group ($p < 0.05$) (Table 3).

Among the symptoms of patients with cerebral infarction, hemiplegia was the highest at 76.8%. Followed by facial paralysis, aphasia, and headache with respect ratio is 26.8, 21.4, and 19.6%. In addition, patients may have dizzy (10.7%), sensory disturbances (14.3%), and nausea (5.4%) (Figure 1).

Table 4 describes the characteristics of NIHSS and mRankin of study groups (compare between OSAS and non-OSAS groups). NIHSS in the OSAS group was statically higher than in the non-OSAS group (The median NIHSS for each group was 5 vs. 2) ($p < 0.05$) Similarly, the mRankin score in the OSAS group was also statistically higher than in the non-OSAS group (48.21 and 23.21% vs. 26.79 and 1.79%) ($p < 0.05$) (Table 4).

Figure 2 summarizes the clinical symptoms of obstructive sleep apnea including loud snoring, non-breathing during sleep, excessive daytime sleepiness, waking up a lot during the night, morning headache, and poor memory. Loud snoring during sleep accounted for the highest rate (38/56 patients); ~80% of patients in the OSAS group have loud snoring.

Correlation between AHI and neck circumference, BMI, LDL cholesterol, NIHSS score, mRankin

The main objective of this study is to investigate the relationship between obstructive sleep apnea syndrome and the severity of cerebral infarction. Therefore, we analyzed in relation to risk factors such as neck circumference, BMI, LDL cholesterol, mRankin, and NIHSS. The results are shown by linear equations. There is a moderate positive correlation between AHI and neck circumference ($r = 0.4$, $p < 0.05$) (Figure 3). There are similar results between AHI and BMI ($r = 0.38$, $p < 0.05$) (Figure 4); AHI and LDL Cholesterol ($r = 0.38$, $p < 0.05$) (Figure 5); AHI and mRankin ($r = 0.49$, $p < 0.05$) (Figure 6). Especially, we find a strong positive correlation between AHI and NIHSS ($r = 0.53$, $p < 0.05$) (Figure 7).

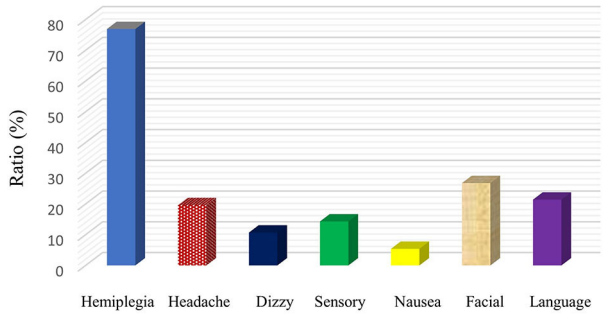

FIGURE 1
Clinical symptoms on admission.

TABLE 4 Characteristics of NIHSS.

		Non-OSAS		OSAS		*p*
		n	%	*n*	%	
NIHSS	0–4	15	26.8	18	32.1	**<0.05**
	5–14	1	1.8	22	39.3	
	Median	2		5		**<0.05**
	Variation	0–5		1–12		
mRankin score	0–2	15	26.79	27	48.21	**<0.05**
	>2	1	1.79	13	23.21	
	Trung bình	0.44 ± 0.81		1.98 ± 1.12		**<0.05**

NIHSS, National Institutes of Health Stroke Scale. The bold values mean statistically significant difference (with $p < 0.05$).

Discussion

General and clinical characteristics

Regarding the general characteristics of the study subjects, this study was conducted on 56 patients with cerebral infarction with an average age of 67.70 ± 11.07. The study did not show a statistically

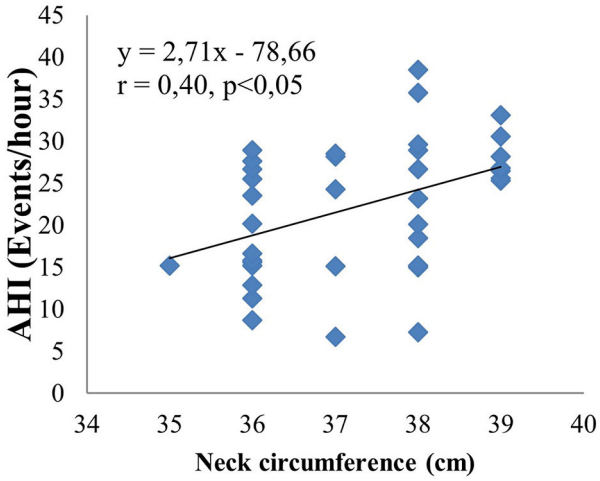

FIGURE 3
Correlation between AHI and neck circumference.

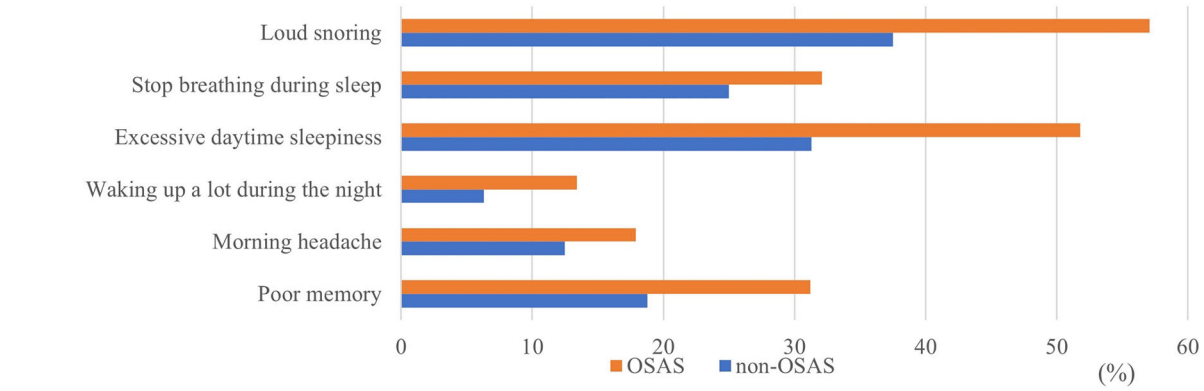

FIGURE 2
Symptoms of obstructive sleep apnea.

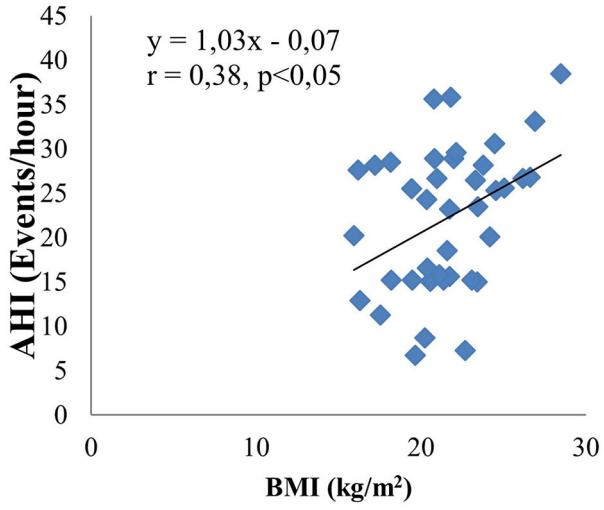

FIGURE 4
Correlation between AHI and BMI.

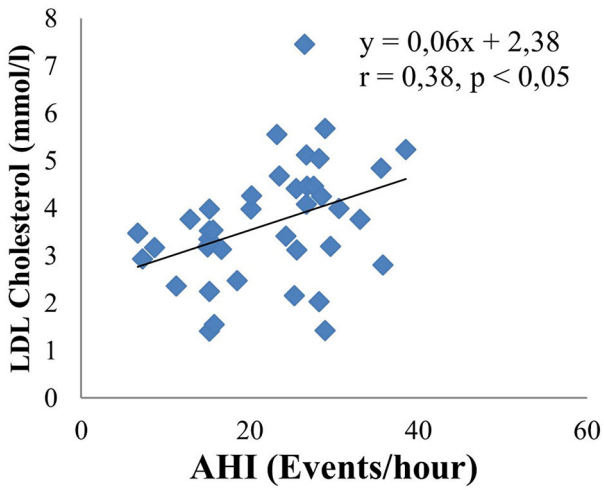

FIGURE 5
Correlation between AHI and LDL Cholesterol.

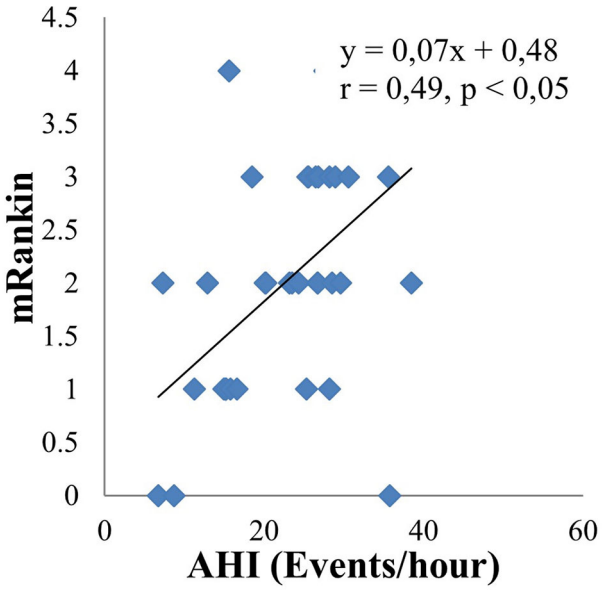

FIGURE 6
Correlation between AHI and mRankin.

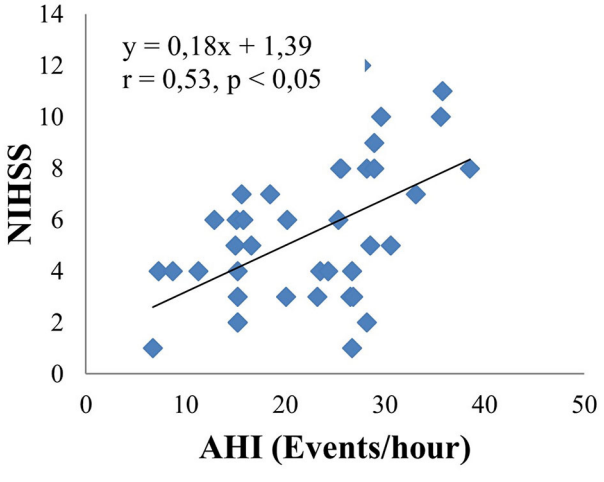

FIGURE 7
Correlation between AHI and NIHSS.

significant age difference between the OSAS and non-OSAS groups. Age is also one of the critical risk factors for OSAS. The prevalence of OSA increases with age among adults and tends to stabilize by age 65 (20). In the OSAS group, men account for 53.6%. This result is consistent with several studies, such as the study of Asha'ari Zamzil Amin with a male-female ratio of 80/38, and author Sy Duong Quy gave the result that this ratio is 1.2/1 (2, 21). This result has been documented in the literature as the prevalence of OSA is higher in men than in women, and most population-based studies show that the prevalence of OSA is 2 to 3 times higher in men (22, 23). In fact, women often do not present with the classic symptoms of OSA (loud snoring, sleep apnea, and excessive sleepiness). They mainly complain of a lack of energy and fatigue. Sex hormones may have an important role in the pathogenesis of OSA. Evidence is that OSA is more common in post-menopausal women than in premenopausal women, and hormone replacement therapy for post-menopausal women may protect them against the disorder (24).

Our study has the result that BMI in the OSAS group is 21.56 ± 2.98 (kg/m^2), statistically higher than the non-OSAS group [19.09 ± 2.37 (kg/m^2) ($p < 0.05$)]. This result is similar to Duong Quy Sy's study with the mean BMI in the group with OSAS of 23.85 ± 3.43 (kg/m^2), which is statistically significantly higher than in the non-OSAS group with 21.58 ± 2.98 (kg/m^2) ($p < 0.05$) (2). This result shows the relation between BMI and OSAS, which is also consistent with the research results of Carmine F. et al. by finding a moderate positive correlation between BMI and AHI ($r = 0.33$, $p < 0.001$) (25). Overweight and obesity increase the severity of

OSAS because fat accumulation in some areas, especially around the upper respiratory tract, easily leads to the risk of fat deposition near the pharynx causing narrowing of the upper airway; changes in neural compensatory mechanisms to maintain airway openness; the respiratory control system is unstable. In our study, the rate of overweight and obesity was 25% (23.2% in the OSAS group and 1.8% in the non-OSAS, $p < 0.05$).

In our study, the neck circumference in the OSAS group was 37.25 ± 1.92 (cm) higher than in the non-OSAS group. This result can be explained because neck circumference is one of the manifestations of upper body fat, which is one of the important factors of OSAS. Therefore, neck circumference is a better predictor of OSAS than waist circumference and other metabolic syndrome factors. However, the direct role of neck circumference in the pathogenesis of OSAS has not been clearly defined (26).

The lowest median SpO_2 in the OSAS group was statistically significantly lower than that in the non-OSAS group ($p < 0.05$). The background SpO_2 in the OSAS group was also significantly lower than that of the non-OSAS group ($p < 0.05$). The results are quite similar to a few other studies around the world. Following Mattaliano et al., the background SpO_2 in the OSAS group (+) was 92.7 ± 2.9, which was statistically significantly lower than the OSAS group (–) was 94.0 ± 2.2. Meanwhile, the lowest SpO_2 in the OSAS group (+) was 81.9 ± 7.6, which was statistically significant compared with the OSAS group (–) was 87.7 ± 4.3 ($p < 0.01$) (10).

Snoring is one of the symptoms of OSAS and has the highest prevalence in this study. It is a sound produced by the vibration of the upper respiratory tract soft tissues during sleep. A 14-year longitudinal study found that 13% of adults snore. Factors associated with snoring include male gender, obesity, smoking, and asthma. In addition, snoring is strongly associated with increased all-cause mortality (27). The study's results also have shown that excessive daytime sleepiness is higher in the OSAS group than in the non-OSAS group. This result is an important and common symptom of OSAS. Daytime sleepiness can mean losing alertness or falling asleep under inappropriate circumstances. People are considered excessively sleepy when they are not alert enough to perform the tasks of daily living.

Relationship between obstructive sleep apnea syndrome and cerebral infarction

In this study, diastolic blood pressure in the OSAS group was statistically higher than in the non-OSAS group. The study of Chen et al. in the chronic cerebral infarction group showed similar results that there was a statistical difference in hypertension between the group with OSAS and the control group (28). This result can be explained by the fact that OSAS patients with apnea sleep lead to increased sympathetic activities and endothelial dysfunction, ultimately resulting in vascular structural modifications, vasoconstriction, cardiovascular events, and hypertension (14).

The NIHSS and mRankin scores were statistically higher in the OSAS group than in the non-OSAS group. The study of Ahn et al. showed that the mRankin score in the OSAS group (1.68 ± 1.89) was statistically higher than in the non-OSAS group (1.18 ± 1.65) and this result is quite similar to our study.

Obstructive sleep apnea Syndrome is independently associated with hypertension, insulin resistance, impaired glucose tolerance, and dyslipidemia. Our results show that the concentration of total cholesterol, LDL-C in the OSAS group was statistically significantly higher than that in the non-OSAS group. The remaining indexes such as fasting intravenous glucose, HDL cholesterol, and triglyceride had no statistically significant differences between the two groups. There is a statistically significant mean positive correlation between LDL-C and AHI with the regression equation: $y = 0.06x + 2.38$; $r = 0.38$; $p < 0.05$. Analyzing the multivariate correlation between AHI and other factors, we found that if AHI increased by 1 event/hour, the NIHSS increased by 0.23 points. In contrast, when LDL cholesterol increased by 1 mmol/l, the NIHSS decreased by 0.78 points. In addition, the study also showed a strong positive correlation between AHI and NIHSS ($r = 0.53$, $p < 0.05$), as well as a moderate positive correlation between AHI and mRankin score ($r = 0.49$, $p < 0.05$). Therefore, it shows a correlation between the severity of sleep apnea syndrome and the severity and disability of patients with cerebral infarction through the NIHSS and mRankin scales. The mechanism of that combination can be explained as follows:

First, apnea and the resulting persistent O_2 deficiency in patients with OSAS causes increased sympathetic tone and endothelial dysfunction. Vascular remodeling and vasoconstriction lead to cardiovascular complications, nocturnal hypertension, and other cardiovascular dysfunctions.

Second, oxidative stress which is produced by repeated hypoxemia and episodes of apnea leads to endothelial dysfunction and the rise of proinflammatory chemical mediators, such as Cyclooxygenase (COX-2), tumor necrosis factor-α (TNF-α), Interleukins and other pro-inflammatory chemical mediators. It easily leads to the initiation and progression of atherosclerotic plaque blood and insulin resistance.

Third, hypertension and arrhythmia, carotid intima-media thickness, and carotid atherosclerosis in the sleep apnea group are more common than in the normal group. Gonzaga found that the risk of hypertension was strongly associated with the potential severity of OSA after 4 years of follow-up (29). The blood flow in the middle cerebral artery remains unchanged due to the reaction of Angiotensin II, Noradrensine, Isoproterenol, and Bradykinin. Simultaneously, inhibition of plasminogen-1 and platelet activation leads to increased risk factors for vascular thrombosis.

Conclusion

There is a significant proportion of cerebral infarction patients with OSA and this should be considered if the patient has symptoms such as loud snoring during sleep, excessive daytime sleepiness and large neck circumference, and high BMI. In addition, OSA is also a factor in predicting the severity of ischemic stroke patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Hue University of Medicine and Pharmacy. The patients/participants provided their written informed consent to participate in this study.

Author contributions

QD-M, TH-A, and SD-Q conceived the study and designed the study protocol. QD-M organized, performed the study investigations, and supported the recruitment of the patients. TH-A performed the statistical analyses. QD-M, TH-A, and NN-T-Y wrote the first draft of the manuscript. All authors have made substantial contributions, critically revised the manuscript for important intellectual content, and read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1132014/full#supplementary-material

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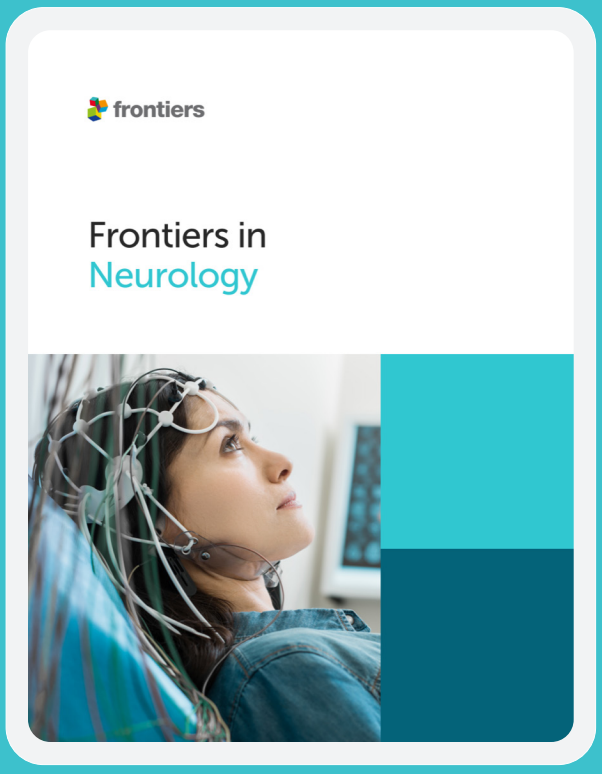

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