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Detection for pediatric obstructive sleep apnea syndrome: Role of objective and subjective measures

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以主觀及客觀臨床評估
偵測兒童阻塞性睡眠呼吸中止

Detection for pediatric obstructive sleep apnea syndrome: Role of objective and subjective measures

本論文係康焜泰君（學號 R01849038）在國立臺灣大學公共衛生學院流行病學與預防醫學研究所預防醫學組完成之碩士學位論文，於民國 103 年 6 月 30 日承下列考試委員審查通過及口試及格，特此證明

口試委員：

李永銘 （簽名）

（指導教授）

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回憶起剛進入流預所的青澀似乎還記憶猶新，時光飛逝，一轉眼碩士班的學業即將畫上句點，在工作、家庭、與研究中奔波，很慶幸一路上有貴人相助。

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中文摘要

背景 兒童阻塞性睡眠呼吸中止症候群是指在兒童在睡眠中因呼吸道阻塞而導致的呼吸中止。診斷主要是依據臨床病史合併適當的檢查，目前仍以睡眠多項生理檢查為診斷的黃金標準。對兒童進行客觀及主觀的臨床評估可提供臨床醫師決策的參考。

目的 評估客觀及主觀臨床評估在偵測兒童阻塞性睡眠呼吸中止症的診斷能力；並比較客觀評估、主觀評估、及合併主客觀評估偵測兒童阻塞性睡眠呼吸中止症的能力和臨床應用上的差異。

研究設計 橫斷性研究。

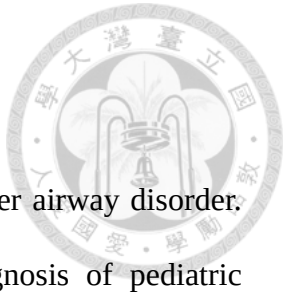
研究材料及方法 本研究受試者的年齡層介於 2 到 18 歲。客觀的臨床評估包括扁桃腺大小，腺樣體大小，和孩童肥胖的評估：扁桃腺是由耳鼻喉科醫師使用 Brodsky 分級方法去分級，腺樣體的大小是量測受試者側面的測顱 X 光片，並以 Fujioka 方法測定，肥胖是測量受試者的身體質量指數百分位來決定。主觀的臨床評估使用標準化的記錄表格，由照護者填寫受試者相關的症狀。顯著與兒童阻塞性睡眠呼吸中止症有關的客觀評估納入客觀模型，顯著與兒童阻塞性睡眠呼吸中止症有關的主觀評估納入主觀模型，在混合模型中包含了與兒童阻塞性睡眠呼吸中止症有顯著相關性的客觀和主觀臨床評估。兒童阻塞性睡眠呼吸中止症的診斷依據睡眠多項生理檢查的結果加以診斷。客觀模型、主觀模型及混合模型在偵測兒童阻塞性睡眠呼吸中止症的能力是評估模型的配適度(model fit)、鑑別度(discrimination，C 指數)、校準度(calibration，Hosmer-Lemeshow 檢定)、及重分類(reclassification)的能力。並使用 leave-one-out、拔靴法(bootstrap)、以及 k-fold 方法對模型進行內部驗證(internal validation)。

結果 總共有 222 名受試者納入本研究。客觀模型的參數包含扁桃腺肥大，腺樣體肥大以及肥胖；而主觀模型的參數包含打鼾的頻率，打鼾的時間，夜晚有驚醒現象，以及照護者發現受試者有呼吸中止現象；混合模型則合併了以上的參數。在模型配適度的部分，經由卡方檢定顯示在客觀模型，主觀模型和混合模型均呈現顯著($P < 0.001$)。在鑑別度的部分，混合模型的 C 指數為 0.84，顯著的優於客觀

模型的 C 指數 0.78 (P=0.0032)及主觀模型的 C 指數 0.72 (P = 0.0001)。在校準度的部分，Hosmer-Lemeshow 的檢定結果顯示客觀模型、主觀模型及混合模型均具有足夠的模型合適性(P>0.05)。在重分類的能力方面，相較於客觀模型，混合模型正確地重新分類 10.3%的病患(P = 0.044)；另一方面，相較於主觀模型，混合模型正確地重新分類 21.9%的病患(P = 0.003)。經由對混合模型的內部驗證顯示模型並未出現明顯過度配適的狀況。

結論　合併主觀和客觀的臨床評估，比起單獨使用客觀評估或主觀評估，在臨床上更能顯著偵測兒童阻塞性睡眠呼吸中止症。本研究的發現提供了相關的理論基礎，即在發展兒童阻塞性睡眠呼吸中止症的篩檢工具時，需要同時合併客觀和主觀的臨床評估去建構此一篩檢工具，以期能達到最大的疾病偵測能力。

關鍵字：腺樣體、兒童、肥胖、扁桃腺、睡眠多項生理檢查、睡眠呼吸中止、症狀評估



Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is an upper airway disorder. Over-night polysomnography is the “gold standard” for the diagnosis of pediatric OSAS. Information from objective and subjective measures for children with OSAS helps clinicians in decision making.

Purpose: To assess diagnostic abilities of objective measures, subjective measures, and combined objective and subjective measures in detecting pediatric obstructive sleep apnea syndrome, and to compare performance difference and clinical utilities between objective measures, subjective measures, and combined objective and subjective measures for detection of pediatric OSAS.

Study Design: Cross-sectional study.

Methods: Children aged 2-18 years were recruited. Children were assessed objectively for tonsil size, adenoid size, and obesity; tonsils were graded by otolaryngologist using the scheme by Brodsky *et al*.; adenoid size was measured based on a lateral cephalometric radiographs (Fujioka method); obesity was determined by a measure of body mass index percentile of each child. Subjective measures for symptoms were recorded using a standard sheet. Objective measures significantly correlated with OSAS were put into the objective model, whereas subjective measures into the subjective model. Accordingly, objective and subjective measures significantly correlated with OSAS were served as the combined model. Diagnosis of OSAS was made by polysomnography. Diagnostic performances of models in detecting OSAS were analyzed by model fit, discrimination (C-index), calibration (Hosmer-Lemeshow test), and reclassification. The model was internal validated using the leave-one-out

cross-validation, bootstrapping method, and k-fold cross-validation.

Results: In total, 222 children were enrolled. Objective model included tonsil hypertrophy, adenoid hypertrophy, and obesity, whereas subjective model included snoring frequency, snoring duration, awaken, and breathing pause. The chi-square test was significant in the objective model, subjective model, and the combined model ($P < 0.001$). The C-index was 0.84 for the combined model, which was significantly differed from that in the objective model (0.78, $P = 0.0032$) and the subjective model (0.72, $P = 0.0001$). The Hosmer-Lemeshow test showed adequate fit ($P > 0.05$) for all models. Compared to objective model or subjective model, the combined model correctly reclassified 10.3% ($P = 0.044$) and 21.9% ($P = 0.003$) of all subjects. Internal validation of the combined model showed fair model performance and no obvious over-fitting.

Conclusions: Overall performance of combined objective and subjective measures, as compared with objective measures or subjective measures alone, offer incremental utility in detecting OSAS. This finding provides the rationale to combine both objective and subjective measures in developing a screen tool for pediatric OSAS.

Key Words: adenoids, child, obesity, palatine tonsil, polysomnography, sleep apnea syndromes, symptom assessment

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1. Introduction

Sleep-disordered breathing (SDB) includes a spectrum of upper airway disorders ranging from primary snoring to obstructive sleep apnea syndrome (OSAS).[1,2] Untreated OSAS in children is associated with cardiovascular,[3] neurocognitive,[4] and somatic growth consequences,[5] while primary snoring (or non-OSAS) in children is usually considered as a benign condition and its management remain controversial.[2] The cause of OSAS in children is mainly due to enlarged tonsils and adenoids which obstruct the airway thereby leading to loss of muscle tone during sleep.[2] Also, child obesity increases the risk of OSAS.[5] Clinically, adenotonsillar hypertrophy and obesity are well recognized to play major roles in children with OSAS.[2,6]

Identifying children with OSAS is of priority concern and is associated with decision-making and treatment recommendation in clinical practice. Hitherto, over-night polysomnography (PSG) is still the “gold standard” for diagnosing pediatric OSAS.[2,7] Overnight PSG involved a detailed evaluation of cardiopulmonary and neurologic parameters in a sleep laboratory and, thus, is time-consuming, costly, entails a long waiting list, and not widely available.[7] Consequently, a simple tool to determine the need of early intervention and referral for over-night sleep studies in children with obstructive sleep disorders is highly desirable.[8-13]

Children were assessed objectively for signs and subjectively for symptoms of OSAS. Physicians are interested in finding an easy and convenient tool to detect pediatric OSAS in clinics. Despite previous studies exploring diagnostic abilities of clinical assessments, diagnostic abilities of subjective measures and objective measures in detecting OSAS in pediatric population, have not been well understood. Therefore, this study elucidates diagnostic abilities of objective measures (i.e., adenoid size, tonsil size,

and obesity), subjective measures (i.e., clinical symptoms), and a combination of both measures in detecting pediatric OSAS.

2. Literature Review

2.1 Pediatric obstructive sleep apnea syndrome

SDB includes a spectrum of upper airway disorders ranging from primary snoring to obstructive sleep apnea syndrome.[1,2,14] The spectrum of disorders can occur throughout from infancy to adolescence.[15] In 1976, Guilleminault *et al*.[16] first describe OSAS in eight children with respect to its clinical symptoms and sleep studies findings. Since then, the social and medical importance of OSAS in children increases worldwide.[17]

Diagnosis

The use of overnight PSG is the gold standard for diagnosis of pediatric OSAS.[18-20] Polysomngraphy involves detailed laboratory evaluations of sleep architectures and cardiopulmonary parameters.[21] The parameters from PSG are scored according to the American Academy of Sleep Medicine standard.[21,22] Among all parameters, apnea/hypopnea index (AHI) is one of the major determinants for the diagnosis of OSAS. The AHI is defined as the number of apneas and hypopneas per hour of total sleep time. Apnea is defined as the presence of continued inspiratory effort associated with >90% decrease in airflow for duration of ≥2 breaths. Hypopnea was defined as ≥50% decrease in airflow for duration of ≥2 breaths associated with arousal, awakening, or reduced arterial oxygen saturation in ≥3%. The diagnosis of pediatric OSAS was defined as the presence of an AHI ≥1 event per hour in the overnight PSG studies.

Epidemiology

The prevalence of OSAS in children has been reported to be 1% to 3%.[23,24] Of note, 9% to 10% of children are habitual snorers.[23,24] This condition may progress to OSAS, and these children suffered from the same risk of complications as children with OSAS.[25]

Pathophysiology

Understanding the pathophysiology of pediatric OSAS permit more precise clinical phenotyping, and therefore improve therapies related to anatomy or neuromuscular compensation. However, the pathophysiology for OSAS in children is complex and not yet fully understood. Recent research suggests that a combination of structural and neuromuscular abnormalities leading to the occurrence OSAS.[26] The most common form of structural anomalies in children is the hypertrophy of the adenoids and tonsils, the fact that is caused by the facial bones grow more slowly than the lymphoid tissue during childhood.[6] Upper airway partial or complete obstructed by adenotonsillar hypertrophy is the main cause of OSAS in children.[26] Other predisposing factors to OSAS in children include craniofacial anomalies,[27] neuromuscular diseases,[28] and obesity.[29,30]

Adverse consequences

The clinical relevance of OSAS in children resides in its association with significant morbidities that affect the cardiovascular, metabolic systems, neurocognitive, and somatic growth.[3,4,5,31] Li *et al*.[3] and Xu *et al*.[32] found OSAS in children was correlated with elevated blood pressure (BP). Horne *et al*.[33] stated that pediatric OSAS increased BP during sleep than control, regardless of OSAS severity. Gozal *et al*.[34] reported coexistence of neurocognitive and endothelial dysfunction in children with OSAS. These findings asserted the correlations between a variety of adverse consequences and pediatric OSAS, and implied that early treatment should be considered in children with OSAS to prevent further complications.[4,35,36]

OSAS in children and growth failure have been shown to correlate with each other.[5,37,38] Of the potential pathways from sleep disturbances to growth failure, growth

hormone hypotheses have received the most attention. Interruptions in slow-wave sleep can lead to impaired growth hormone secretion.[39] Another proposed pathway involves increased energy expenditure during sleep in children with sleep disturbances.[40] Fortunately, underweight children with OSAS been reported to have excellent surgical outcomes and normalized weight status postoperatively.[41]

Treatment

Treatment for children with OSAS can be surgical or nonsurgical, and the choice depends on the underlying pathophysiology.[2,42] Enlarged tonsils and adenoids are the primary causes of pediatric obstructive sleep disorders, explaining why surgical removal of the tonsil and adenoid (Adenotonsillectomy, T&A) is widely recognized as the first-line therapy for pediatric OSAS.[4,41-46] A meta-analysis study of Friedman *et al*.[44] found treatment success for pediatric OSAS with T&A was 59.8%. Other modalities for treatment of pediatric OSAS include continuous positive airway pressure,[47] rapid maxillary expansion,[48] and pharmacologic therapies.[49,50]

2.2 Adenoid size, tonsil size and pediatric OSAS

Adenoid and tonsillar enlargement play major roles in the pathophysiology of pediatric OSAS.[6,26] Significant improvements in PSG have been reported continually in OSAS children after T&A.[41-46] However, previous studies on the correlations between adenoid size, tonsil size, and objective PSG data were contentious.[6,51,52] Nolan J *et al*.[52] systemically reviewed twenty articles comparing tonsil size to over-night polysomnogram, and eleven of twenty studies concluded an association between subjective tonsil size and objective OSAS, whereas nine did not. The association between tonsil size and OSAS severity still require further studies.

While adenoidal hypertrophy is one of the most important causes of nasal obstruction in children, methods for evaluating adenoid size remain controversial and unsatisfactory. Many different ways, including lateral radiographs,[53-57] fiberoptic endoscopy,[58,59] and acoustic rhinometry,[60] have been advocated as reliable in detecting the adenoidal hypertrophy and its connection to upper airway obstruction. Acoustic rhinometry has been used for cross-sectional area evaluation in the nose. The effect of chronic rhinitis, commonly observed in children with sleep disturbances, may interfere adenoid size assessment.[60] Fiberoptic endoscopy is an accurate diagnostic method that allows examiners to obtain a three-dimensional view of adenoid size. However, children need to cooperate in an endoscopic exam, which is not always possible in children with young ages.[59] A lateral cephalometric radiograph is a simple, economical, and reproducible way to measure adenoid size.[61,62] Despite the accuracy of this method has been questioned in view of the fact that these radiographs represent the nasopharynx in only two dimensions,[63,64] a number of authors have found this examination is practical, and gives satisfactory results for children of all ages.[6,53-57] Notably, several radiographic

assessment methods have been reported.[53-57] Among these, the adenoidal-nasopharyngeal (AN) ratio, first described by Fujioka *et al.*,[53] is now the most frequently analyzed radiographic parameter in adenoid size assessment.[6,53,65-67] Related articles proved the AN ratio is an useful and reliable diagnostic tool.[65-67] Caylakli *et al.*[65] identified a significant correlation between the AN ratio and endoscopic examination findings. Lertsburapa *et al.*[66] stated both the AN ratio and endoscopy correlated well with intra-operative exam findings. The use of AN ratio is an easily applicable and non-invasive method that correctly measures adenoid size in patients of all ages.

2.3 Obesity and pediatric OSAS

Obesity among children has received considerable interest in recent years. Pediatric obesity is associated with an increased incidence of various morbidities, including diabetes mellitus, hyperlipidemia, liver and renal disease, reproductive dysfunction, as well as OSAS.[30] Obesity is an independent risk factor for OSAS in children.[5,29] Adipose tissue deposited around the pharynx and neck, along with hypertrophic adenoids and tonsils, largely contribute to obstructive sleep syndrome in obese children.[5,68] Other possible pathophysiological mechanisms contributing to this association include the following: increased critical airway closing pressure, altered chest wall mechanics, and abnormalities of ventilatory control.[30] There is some evidence that OSAS and obesity in children may interact and contribute to metabolic alterations with a potential for significant morbidity,[69] lending the need to development of screening and intervention aiming to reduce the long-term adverse consequences associated with these disorders.

The treatment of OSAS in obese children is more complicated than that in non-obese children. T&A is considered the primary intervention followed by continuous positive airway pressure treatment if OSAS persists.[70] Other methods such as oral appliances, positional therapy, and weight loss may be beneficial for individual subjects.[71]

2.4 Clinical symptoms in detecting pediatric OSAS

Clinical symptoms of pediatric OSAS include snoring, witness breathing pause, mouth breathing, awaken, daytime sleepiness, hyperactive…etc.[8,9,11,14] The preliminary, and most direct question to ask in children with sleep disturbances is "Does your child snore?" [14] Snoring is the most common clinical symptom in children with SDB. Many reports observed high prevalence of snoring in children with OSAS as well as children with primary snoring.[8,9,11,14] Snoring occurs in almost all children with SDB and is the main reason many parents seek medical advice. However, only a proportion of snoring children have OSAS. Children with severe OSAS may also manifest without clear snoring because of prolonged breathing pauses. Consequently, snoring alone is an insensitive indicator of OSAS and it is difficult to make a diagnosis of OSAS based on a history of snoring alone.[14] Brietzke *et al*.[8] systemically reviewed clinical symptoms of SDB in the literatures and found that snoring had a sensitivity of 44% to 97% and specificity of 4% to 58% in detecting pediatric OSAS. Besides, witness breathing pause had a sensitivity of 47% to 88% and specificity of 17% to 90%, whereas mouth breathing had a sensitivity of 29% to 78% and specificity of 27% to 46% in detecting pediatric OSAS.[8] In 2012, Certal *et al*.[9] conducted a diagnostic meta-analysis for clinical assessments for pediatric OSAS. Tonsil size and snoring reported by parents or caregivers had high sensitivity but low specificity. In contrast, excessive daytime somnolence, observed apnea, and difficulty in breathing during sleep had high specificity but low sensitivity. Certal *et al*.[9] used models of a combination of symptoms and signs presented moderate sensitivity (range, 0.04-0.94) and specificity (range, 0.28-0.99). Recently, few studies asserted combinations of both objective and subjective measures might be helpful in screening pediatric OSAS.[11-13]

2.5 Statistical methods for diagnostic performances of models

From a clinical perspective, physicians are interested in finding a new biomarker or predictive mode in order to improve the identification of people at risk of diseases.[72] Therefore, clinicians need to be aware of the various statistical methods used to assess these biomarkers and models and how these are interpreted.[72,73] When a new model or biomarker is developed, it is usually compared with an existing old model based on the four statistical method including global measure of model fit, discrimination,[72] calibration,[74] and reclassification.[75,76]

Global measures of model fit refers to how likely is it that the new model chosen would give rise to the data observed.[72] Two commonly used measures of global fit are the Akaike Information Criterion and the Bayes Information Criterion, which provide information on how likely the model we have chosen would give rise to the data we have observed.[72]

Discriminative properties is to define how well the new model separates individuals who develop the outcome from those who do not.[72] It is usually reported as the C statistic (also known as the C index or the area under the receiver operator characteristic curve). Recently, an alternative measure of discrimination, the integrated discrimination

improvement (IDI) has been proposed, which take into account the difference in predicted risks.[76] The discrimination slope measures the separation between subjects with and without diseases. The IDI is a difference in discrimination slopes between the new and old models.[76]

Calibration explains how close the predicted risks are to the actual observed risks.[72] The calibration of a model can be summarized using the Hosmer-Lemeshow test or

variations of it.[72,74] The Hosmer-Lemeshow test compares the observed number of people with events within prespecified risk groupings (eg, deciles of risk) with the number predicted by the model.[72,74]

Reclassification is used to whether the new model sufficiently changes a person's risk to move them into a different risk category and thus alter treatment decisions.[72] The use of reclassification requires the existence of predefined risk levels at which treatments would change, as well as the existence of effective treatments at different risk levels.[72] In 2008, Pencina *et al*.[76] further proposed the net reclassification improvement (NRI) to facilitate clinical utility of reclassification properties. The NRI is a measure that takes this directional movement into account and thereby focuses on the risks that may be of high interest to the clinician. The NRI is composed of the following 4 components: the proportion of individuals with events who move up or down a category and the proportion of individuals with nonevents who move up or down a category. These 4 components are then combined in the NRI but should also be reported separately to allow clinicians to assess the trade-offs between the reclassification of people who have an event and those who do not.[72,76]

2.6 Gaps of previous studies

Previous studies stated clinical symptoms (subjective measure) or physical examinations (objective measures), as compared with over-night PSG, were not reliable in detecting pediatric OSAS.[8-10] However, diagnostic abilities of subjective measures, objective measures, and combinations of both subjective and objective measures in detecting OSAS in pediatric population, have not been comprehensively evaluated. Furthermore, previous studies assessed model discrimination (C index),[11-13] whereas none examined calibration (for example, Hosmer-Lemeshow goodness-of-fit statistic)[74] or reclassification of OSAS risk in pediatric population.[75,76] The ability to reclassify OSAS risk is recently recognized as a critical metric for assessing diagnostic performances of clinical measures.[75,76]

2.7 Aim of this study

The aim of this study is to elucidate diagnostic abilities of objective measures (i.e., adenoid size, tonsil size, and obesity), subjective measures (i.e., clinical symptoms), and a combination of both measures in detecting pediatric OSAS.

The study conducted in 2 steps: (1) By using objective measures as a basic model, to compare diagnostic performance when adding each subjective measure; and (2) By using objective measures as a basic model, to compare diagnostic performance when adding subjective measures (combined model). Finally, the applications for OSAS risk reclassification (basic model vs. combined model) provided valuable additional insights regarding the clinical usefulness.

3. Methods

3.1 Study population

The study protocol was approved by the Ethics Committee of the National Taiwan University Hospital. From June 2012 to January 2014, children aged 2 to 18 years were recruited. Children were included if they had signs or symptoms suggestive of sleep-disordered breathing including snoring, mouth breathing, and witnessed breath holding for at least 1 month duration.[11] The exclusion criteria were (1) prior tonsil, adenoid, or pharyngeal surgery, (2) cranio-facial anomalies, (3) genetic disorders, neuro-muscular diseases, cognitive deficits, or mental retardation, (4) suboptimal sleep studies (total sleep time <4 hours, or sleep efficiency <60%), (5) children younger 12 months of age. Basic data, including age, gender, and history of nasal allergy, otitis media with effusion, sinusitis or asthma were recorded.

3.2 Objective measures

Objective measures included measures of tonsil size, adenoid size, and obesity.

Tonsil grade

Tonsils were graded according to the scheme proposed by Brodsky:[77] : Grade I) small tonsils confined to the tonsillar pillars; grade II) tonsils that extend just outside the pillars; grade III) tonsils that extend outside the pillars, but do not meet in the midline; grade IV) large tonsils that meet in the midline. Tonsil hypertrophy was defined as grade III or IV tonsils.[77]

Adenoid size

Adenoid size was determined using lateral cephalometric radiographs to measure the adenoidal-nasopharyngeal (AN) ratio. The AN ratio was measured as the ratio of adenoidal depth to nasopharyngeal diameter according to the method of Fujioka *et al.*[53]; an AN ratio ≥0.67 was considered adenoid hypertrophy.[5,6,29]

Obesity

Obesity was determined by a measure of body mass index (BMI) percentile of each child. The weight and height of each child were measured at a sleep lab before PSG studies and BMI was calculated. The age and gender corrected BMI was applied for each children by using established guidelines to define the BMI percentile.[78] The guidelines for BMI in Taiwanese children and adolescents was established by Chen *et al*.[78] Obesity was defined as a BMI higher than the 95th percentile for a child's age and gender.[5,78]

3.3 Subjective measures

Detailed clinical symptoms were taken by using a standard clinical data sheet, which is adapted from that in Xu's study.[11] A standardized clinical data sheet consisted of questions regarding the child's snoring patterns, nighttime and daytime clinical symptoms, as well as other clinical symptoms associated with OSAS. Snoring patterns are snoring frequency and snoring duration of a child. Other nighttime and daytime include diaphoresis, bedwetting, awaken, nightmare, breathing pause, nasal speech, mouth breathing, weight gain, weight loss, daytime sleepiness, poor attention, depression, low self-esteem, shy, hyperactive ,and low academic performance. The questionnaires were administered by clinical physicians and caregivers of our children were asked to complete the standard questionnaire form. All clinical data were verified and recorded during the follow-up visit at a sleep clinic before patient receiving the PSG studies.

3.4 Polysomnography (PSG)

Full-night attained PSG (Embla, Medcare, Ice Land) was done at the sleep lab, with electro-encephalographic activity (C4-A1, C3-A2, O2-A1, and O1-A2); electro-oculogram; chin and tibia electromyogram; oro-nasal airflow by thermocouples and nasal pressure; thoracic and abdominal excursions (respiratory inductive plethysmography); electrocardiogram; snoring sound; body position; and oxygen saturation, following a protocol described elsewhere.[5,6,41,79-82] The sleep stage and respiratory event were scored based on the 2007 American Academy of Sleep Medicine standard.[21,22] All of the sleep studies were analyzed by the principal author to maximize inter- and intra-scorer reliability. Obstructive apnea was defined as the presence of continued inspiratory effort associated with a >90% decrease in airflow for duration of ≥2 breaths. Hypopnea was defined as a ≥50% decrease in airflow for duration of ≥2 breaths associated with arousal, awakening, or reduced arterial oxygen saturation of ≥3%. The disease severity were defined as primary snoring (AHI <1) or OSAS (AHI ≥1). [2,4,6,7,14,15,18,44-46]

3.5 Statistical methods

Data were analyzed using SAS software version 9.3 (SAS Institute, Cary, NC, USA). A P value of less than 0.05 was considered statistically significant. Demographic data, including age, gender, adenoid size, and tonsil size in all subjects were analyzed. Also, parameters in sleep studies, including AHI, mean oxygen saturation ($MeanSaO_2$), and minimum oxygen saturation ($MinSaO_2$) in all subjects were analyzed. Categorical data were expressed as the number and percentage. Continuous data were expressed as mean, standard deviation, minimum, maximum, the first quartile, the second quartile, and the third quartile.

Objective measures (i.e., tonsil hypertrophy, adenoid hypertrophy, obesity) and subjective measures (e.g., snoring frequency, snoring duration, breathing pause) in all subjects were recorded and analyzed. Data were expressed as the number and percentage.

Children with AHI ≥1 were categorized into the OSAS group, while those with AHI <1 into the non-OSAS group. Comparisons of demographics, sleep studies, objective measures, and subjective measures between the OSAS and the non-OSAS group were made. Categorical variables between the OSAS group and the non-OSAS group were compared using Chi-square test, while continuous variables between the OSAS group and the non-OSAS group were compared using independent sample t-test.

The OSAS risk for objective and subjective measures was analyzed. Objective measures or subjective measures that is significantly correlated with pediatric OSAS were put into the multiple logistic regression model. The B value, P value, adjusted odds ratios and 95% confidence interval of clinical measures in detecting risk of pediatric OSAS were all estimated by multiple logistic regression model.

Collinearity diagnostics of the objective measures and subjective measures in detecting pediatric OSAS were analyzed. Multicollinearity refers to a situation in which two or more explanatory variables in a multiple regression model are highly linearly related. In statistics, the variance inflation factor (VIF) and the tolerance quantifies the severity of multicollinearity. The VIF provides an index that measures how much the variance (the square of the estimate's standard deviation) of an estimated regression coefficient is increased because of collinearity. The tolerance is just the reciprocal of the VIF. Analyze the magnitude of multicollinearity by considering the size of the VIF. A common rule is that if VIF >10 then multicollinearity is high.[83]

3.5.1 Objective model vs. subjective model vs. combined model

Objective measures (i.e., tonsil size, adenoid size, and obesity) which were significantly correlated with pediatric OSAS were put into the objective model. Similarly, items of clinical symptoms which were significantly correlated with pediatric OSAS were selected to put into the subjective model. Combined model included both subjective measures and objective measures that were significantly correlated with pediatric OSAS.

3.5.2 Global measures of model fit

The global measure of model fit were assessed using the likelihood ratio Chi-square statistic and Nagelkerke R square statistic, with a higher value indicated a better model fit. Additionally, for models, the Akaike information criterion and Bayes information criterion were analyzed,[84] which were statistical estimates of the trade-off between the likelihood of a model against its complexity, with a lower value indicating a better model fit. Global measure of model fit was estimated in objective model, objective model adding one subjective measure, subjective model, and the combined model.

3.5.3 Discrimination

Discrimination is the ability of a model to separate those with OSAS from those without OSAS. The C index is an estimate for the area under a receiver operating characteristic (ROC) curve for logistic regression model,[85] which is an overall summary of diagnostic accuracy. Additionally, the difference between the two ROC curves derived from two different models administered on the same set of patients was compared and the P-value for the difference was estimated. A P value <0.05 indicating

that the two compared areas are significantly different.[85]

The IDI has been proposed recently, which take into account the difference in predicted risks. The discrimination slope measures the separation between subjects with OSAS and subjects without OSAS in terms of the average predicted risks for these 2 groups. The IDI is a difference in discrimination slopes between the new and old models.

The IDI is estimated by the formula from Pencina *et al*.[76]

$$\widehat{\mathrm{IDI}} = (\overline{\hat{p}}_{\mathrm{new,events}} - \overline{\hat{p}}_{\mathrm{new,nonevents}}) - (\overline{\hat{p}}_{\mathrm{old,events}} - \overline{\hat{p}}_{\mathrm{old,nonevents}})$$

$\overline{\hat{p}}_{\mathrm{new,events}}$ = the mean of the new model-based predicted probabilities for OSAS group

$\overline{\hat{p}}_{\mathrm{new,nonevents}}$ = the mean of the new model-based predicted probabilities for non-OSAS group

$\overline{\hat{p}}_{\mathrm{old,events}}$ = the mean of the old model-based predicted probabilities for OSAS group

$\overline{\hat{p}}_{\mathrm{old,nonevents}}$ = the mean of the old model-based predicted probabilities for non-OSAS group

The standard deviation of OSAS ($\widehat{\mathrm{se}}_{\mathrm{events}}$) is calculated as the standard error of paired differences of new and old model-based predicted probabilities across the OSAS subjects ($\hat{p}_{\mathrm{new,events}} - \hat{p}_{\mathrm{old,events}}$). The corresponding estimator was obtained for non-OSAS subjects. The null hypothesis (IDI=0) is tested using Z test.

$$z = \frac{\widehat{\mathrm{IDI}}}{\sqrt{(\widehat{\mathrm{se}}_{\mathrm{events}})^2 + (\widehat{\mathrm{se}}_{\mathrm{nonevents}})^2}}$$

3.5.4 Calibration

Calibration evaluates the degree of correspondence between the predicted probability of OSAS based on a model and the observed OSAS and is typical evaluated with the Hosmer-Lemeshow statistic.[74] The Hosmer-Lemeshow test statistic follows a Chi-square distribution and a small value indicates a good calibration. A $P < 0.05$ indicates significant lack of calibration.

3.5.5 Reclassification

The reclassification of OSAS risk was evaluated by comparing predicted risk estimates based on objective model with and without adding subjective measure. Reclassification rates were evaluated separately in individuals who had OSAS and in those who do not.[75,76,86] The predicted OSAS probabilities were grouped into risk categories >50% and <50% based on selected models. Upwards movement in categories in individuals who had OSAS indicates improved classification, whereas any downward movement in those with OSAS implies worse reclassification. Similarly, a downward movement in individuals who do not have OSAS indicates improved classification, whereas any upward movement in those without OSAS implies worse reclassification. The NRI is then calculated by summing the reclassification improvements for those with OSAS and those without OSAS. The statistical testing for significance of NRI is calculated according to the formula by Pencina *et al.*[76]

The formula from Pencina *et al.*[76] is listed below.

$$\hat{P}(\text{up}|D=1) = \hat{p}_{\text{up,events}} = \frac{\#\text{ events moving up}}{\#\text{ events}}$$

$$\hat{P}(\text{down}|D=1) = \hat{p}_{\text{down,events}} = \frac{\#\text{ events moving down}}{\#\text{ events}}$$

$$\hat{P}(\text{up}|D=0) = \hat{p}_{\text{up,nonevents}} = \frac{\#\text{ nonevents moving up}}{\#\text{ nonevents}}$$

$$\hat{P}(\text{down}|D=0) = \hat{p}_{\text{down,nonevents}} = \frac{\#\text{nonevents moving down}}{\#\text{ nonevents}}$$

The NRI is estimated as

$$\widehat{\text{NRI}} = (\hat{p}_{\text{up,events}} - \hat{p}_{\text{down,events}}) - (\hat{p}_{\text{up,nonevents}} - \hat{p}_{\text{down,nonevents}})$$

Assuming independence between event (OSAS) and non-event (non-OSAS) individuals and following McNemar's logic for significance testing in correlated proportions (and using the properties of multinomial distribution), a simple asymptotic test for the null hypothesis of NRI=0 is tested (using Z test).

$$z = \frac{\widehat{\text{NRI}}}{\sqrt{\frac{\hat{p}_{\text{up,events}} + \hat{p}_{\text{down,events}}}{\#\text{ events}} + \frac{\hat{p}_{\text{up,nonevents}} + \hat{p}_{\text{down,nonevents}}}{\#\text{ nonevents}}}}$$

Two-sided P value of <0.05 were considered statistically significant.

3.5.6 Validation

Internal validation of the model was conducted by using the leave-one-out method, bootstrapping method, and k-fold cross-validation.

Leave-one-out cross-validation

Leave-one-out cross-validation involves using a single observation from the original sample as the validation data, and the remaining observations as the training data. This is repeated such that each observation in the sample is used once as the validation data. The concordance C-index of the combined model was internal validated by the leave-one-out cross-validation method.[87]

Bootstrap cross-validation

The C-index as a measure for the area under the receiver operating characteristic (ROC) curve represents the diagnostic accuracy of the model. Internal validation of the concordance C-index of the combined model was performed by the bootstrapping method of 100, 200, and 500 iterations.[88]

K-fold cross-validation

In k-fold cross-validation, the original sample is randomly partitioned into k equal size subsamples. Of the k subsamples, a single subsample is retained as the validation data for testing the model, and the remaining k-1 subsamples are used as training data. The cross-validation process is then repeated k times (the folds), with each of the k subsamples used exactly once as the validation data.[89] K-fold cross-validation of the concordance C-index of the combined model was performed by partitioning the original sample into 3-fold, 5-fold, and 10 fold subsamples.

4. Results

4.1 Study population

Initially, 287 subjects were identified for possible inclusion. Fifty-three children were excluded due to incomplete records or PSG studies. Twelve children were excluded due to co-morbidities that met exclusion criteria, including 7 children with craniofacial anomaly and 5 children with neuromuscular disease. In total, 222 subjects were enrolled into the final analysis (**Figure 1**).

Table 1, 2, and 3 listed demographics in all subjects. Table 1 listed categorical variables in all subjects. In this study group, boys comprised 67.1 % (149/222). Forty-eight children (21.6%) were obese, and 174 (78.4%) were non-obese; 126 (56.8%) subjects had tonsil hypertrophy, and 134 (60.4%) subjects had adenoid hypertrophy. Fourteen (6.3%) subjects had grade 1 tonsil, 82 (36.9%) had grade 2 tonsil, 82 (36.9%) had grade 3 tonsil, and 44 (19.8%) had grade 4 tonsil. Among all subjects, 106 (47.7%) met the criteria for primary snoring, while 116 (52.3%) out of 222 met the criteria for pediatric OSAS.

Table 2 showed continuous variables in all subjects. Mean age of study participants was 7.3±3.7 years (median: 6.5 years; 25th to 75th percentile: 4.7 to 9.4 years). The youngest age was 1.4 years, and the oldest age is 17.8 years. The mean weight of all subjects was 29.2 ± 16.2 kg (median: 22.9 kg; 25th to 75th percentile: 18.0 to 34.7 kg). The weight in all subjects ranged from 10 to 93 kg. The mean height of all subjects was 122.2 ± 21.7 cm (median: 119.5 cm; 25th to 75th percentile: 106.8 to 136.3 cm). The height in all subjects ranged from 79 to 185 cm. The mean BMI was 18.1 ± 3.9 kg/m^2 (median: 16.8 kg/m^2; 25th to 75th percentile: 15.3 to 20.4 kg/m^2). The BMI in all subjects ranged from 11.4 to 31.2 kg/m^2. The mean BMI percentile was 62.2 ± 30.7

centile (median: 64.7 centile; 25th to 75th percentile: 37.8 to 92.3 centile). The BMI percentile in all subjects ranged from 2 to 99 centile. The mean AN ratio was 0.69 ± 0.16 (median: 0.73; 25th to 75th percentile: 0.58 to 0.83). The AN ratio in all subjects ranged from 0.30 to 0.95. Sleep data from PSG studies showed the mean AHI was 5.4 ± 13.0 events/hour (median: 1.0 events/hour; 25th to 75th percentile: 0.3 to 3.4 events/hour). The AHI in all subjects ranged from 0 to 130.5 events/hour. The mean of mean oxygen saturation ($MeanSaO_2$) was 97.2 ± 2.2 % (median: 97.7 %; 25th to 75th percentile: 97 to 98 %). The $MeanSaO_2$ in all subjects ranged from 70.0 to 99.4 %. The mean of minimum oxygen saturation ($MinSaO_2$) was 88.8 ± 6.1 % (median: 91 %; 25th to 75th percentile: 86 to 93 %). The $MinSaO_2$ in all subjects ranged from 50 to 97 %.

Objective measures and subjective measures in all subjects were demonstrated in **table 3**. Of objective measures in all subjects, 56.8% had tonsil hypertrophy, 60.4% had adenoid hypertrophy, and 21.6% were obese. Of subjective measures in all subjects, the three main subjective symptoms were snoring (93.2%), mouth breathing (80.6%), and nasal speech (80.2%). For snoring duration and snoring frequency, 144 (64.9%) children had snoring more than 5 nights per week and 166 (74.8%) children had snoring more than 3 months. Other nighttime and daytime symptoms in all subjects included poor attention problem (41.9%), nighttime awaken (32.0%), witness of breathing pause by caregivers (27.9%), nightmare (27.0%), diaphoresis (23.9%), hyperactive (22.5%), low academic performance (17.6%), weight gain (17.1%), daytime sleepiness (15.8%), shy (14.0%), bedwetting (12.2%), low self-esteem (8.1%), weight loss (6.3%), and depression (1.4%).

Table 4 listed correlation between age (in year) and adenotonsillar size. The tonsil size and age were not significantly correlated with each other in either the OSAS (P =

0.062) or non-OSAS group (P = 0.3). In contrast, the adenoid size inversely correlated with age in both the OSAS (P <0.001) and non-OSAS group (P <0.001).

Table 5 compared adenotonsillar size and age groups in the OSAS and non-OSAS group. The tonsil size did not significantly differed among different age groups in either the OSAS (P = 0.086) and non-OSAS group (P = 0.612). In contrast, the adenoid size inversely correlated with age groups in both the OSAS (P <0.001) and non-OSAS group (P <0.001).

Table 6 listed comparisons of the demographic data between the OSAS group and the non-OSAS group. Age (7.6 ± 4.0 vs. 7.1 ± 3.2 years, p = 0.355), gender (Boys 63.8 vs. 70.8 %, p = 0.270), height (123.0 ± 23.3 *vs.* 121.3 ± 19.9 cm, p = 0.543) and BMI percentile (64.9 ± 31.0 *vs.* 59.3 ± 30.3 centile, p = 0.175) did not significant differ between these two groups. The OSAS group had significant higher weight (31.5 ± 18.9 *vs.* 26.8 ± 12.4 kg, p = 0.03) and higher BMI (18.9 ± 4.6 *vs.* 17.3 ± 2.8 kg/m^2, p = 0.002) than the non-OSAS group. Among sleep parameters recorded by overnight PSG, the OSA group had higher AHI (9.9 ± 16.8 *vs.* 0.4 ± 0.3 events/hour, p <0.001) than the non-OSAS group. Children with OSAS also had lower $MeanSaO_2$ (96.6 ± 2.8 *vs.* 97.7 ± 0.9 %, p <0.001) and $MinSaO_2$ (86.1 ± 6.8 *vs.* 91.7 ± 3.4 %, p = 0.001) than children without OSAS.

4.2 Clinical measures in detecting pediatric obstructive sleep apnea syndrome

Table 7 compared objective and subjective measures between the OSAS and the non-OSAS group. Table 7 listed the sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio of each objective and subjective clinical measures in detecting pediatric OSAS. For objective measures, tonsil hypertrophy (76.7% *vs.* 34.9%, p <0.001) and adenoid hypertrophy (75.0% *vs.* 44.3%, p <0.001) were more prevalent in children with OSAS than without OSAS. Obesity was also correlated with OSAS (28.4% *vs.* 14.2%, p = 0.011). Objective measures of tonsil hypertrophy and adenoid hypertrophy had a high sensitivity (76.7% and 75.0%), whereas obesity had a low sensitivity (28.4%) but high specificity (85.8%) in predicting pediatric OSAS. For subjective measures, the three leading clinical symptoms were snoring (93.2%), mouth breathing (80.6%), and nasal speech (80.2%). The clinical symptoms of snoring more than 5 nights per week, snoring more than 3 months, breathing pause, and awaken at night were significantly correlated with pediatric OSAS (76.7% *vs.* 51.9%, p <0.001; 83.6% *vs.* 65.1%, p = 0.002; 42.2% *vs.* 12.3%, p <0.001; 37.9% *vs.* 25.5%, p = 0.048, respectively). Snoring more than 5 nights per week and snoring more than 3 months had a high sensitivity in detecting OSAS (76.7% and 83.6%, respectively). Witness breathing pause and awaken at night had a high specificity (87.7% and 74.5%) but had a low sensitivity (42.2% and 37.9%) in detecting OSAS. Symptoms of diaphoresis, bedwetting, mouth breathing, sleepiness, shy, and low academic performance were also more frequent in the OSAS group than in the non-OSAS group but statistically insignificant.

A multiple logistic regression model was applied to analyze the associations between

clinical measures and OSAS risk (**Table 8**). In a multiple logistic regression model, tonsil hypertrophy (OR=7.2; 95% CI 3.5-14.8, p <0.001), adenoid hypertrophy (OR = 2.0; 95% CI 1.0-3.9, p = 0.047), awaken (OR = 2.1; 95% CI 1.0-4.4, p = 0.043), and breathing pause (OR = 5.7; 95% CI 2.4-13.5, p <0.001) significantly increased the risk of OSAS in children, whereas obesity (OR = 2.1; 95% CI 0.9-4.8, p = 0.068), snoring > 5 nights/week (OR = 1.4; 95% CI 0.7-2.9, p = 0.382) and snoring > 3month (OR = 1.3; 95% CI 0.6-3.1, p = 0.475) was not significantly correlated with pediatric OSAS.

Multicolinearity of the model in detecting pediatric OSAS were examined using the tolerance and the VIF. **Table 9** listed the collinearity diagnostics of the objective measures and subjective measures in detecting pediatric OSAS. If none of the VIFs are greater than 10, collinearity is not a problem. The VIF values were ranged from 1.02 to 1.29 (**Table 9**). Since the VIF was far below 10, collinearity in objective or subjective model in detecting pediatric OSAS was not thought likely to occur.

4.3 Effects of adding each subjective measure on objective measures

The objective model includes objective measures significantly correlated with pediatric OSAS (i.e., tonsil hypertrophy, adenoid hypertrophy, and obesity), and was used as the basic model. Of note, only subjective measures that significantly correlated with pediatric OSAS (i.e., snoring >5 nights/week, snoring >3month, breathing pause, and awaken) were used to add into the basic model. **Table 10** showed the global model fit when adding one subjective measure on objective model in detecting pediatric OSAS. The likelihood ratio chi-square test was highly statistically significant in the basic model as well as models containing basic model adding one subjective measure ($P < 0.001$). Comparing basic model adding one subjective measure, the R^2 was highest and the Bayes information criterion was lowest when adding “breathing pause” to the basic model. The C-index for the basic model was 0.775, and ranged from 0.788 to 0.822 when adding one subjective measure (**Table 11 and Figure 2**). As expected, the C-index was highest when adding “breathing pause” to the basic model. Comparing the basic model, the differences in the C-index were around 0.01 for adding “snoring >5 nights/week”, “snoring >3month”, “breathing pause”, and “awaken” to the basic model, but were 0.047 for adding “breathing pause”. Additionally, the P value for the difference in the C-index was only significant when adding “breathing pause” to the basic model ($P = 0.001$). The Hosmer–Lemeshow test for basic model and basic model adding one subjective measure showed adequate fit for models in detecting pediatric OSAS ($P >0.05$) (**Table 11**).

Table 12 showed the IDI of each subjective measure adding on objective model to detect pediatric OSAS. By using the objective model, the mean predicted probability of OSAS was 0.636, and the mean predicted probability of OSAS was 0.398. The

discrimination slope of the objective model between the OSAS and the non-OSAS subjects was 0.238. The discrimination slope of the objective model adding “snoring frequency” was 0.259. The IDI for the objective model adding “snoring frequency” was 2.1% (P = 0.029). The discrimination slope of the objective model adding “snoring duration” was 0.255. The IDI for the objective model adding “snoring duration” was 1.7% (P = 0.062). The discrimination slope of the objective model adding “awaken” was 0.255. The IDI for the objective model adding “awaken” was 1.7% (P = 0.048). The discrimination slope of the objective model adding “breathing pause” was 0.320. The IDI for the objective model adding “breathing pause” was 8.2% (P <0.001).

Reclassification of OSAS risk was examined by using basic model with and without each subjective measure in turn, that is, comparing basic model with the basic model adding one subjective measure. For pediatric OSAS, relevant strata are categories as <50% (low risk) and >50% (high risk) groups. The basic model with “snoring frequency” categorized 3.4% OSAS subjects into the high risk group (improved reclassification), and 4.7% non-OSAS subjects into the high risk group (worse reclassification). The NRI offered by addition of “snoring frequency” to the basic model was -1.3% (**Table 13**).

The basic model with “snoring duration” categorized 6.0% OSAS subjects into the high risk group (improved reclassification), and 5.7% non-OSAS subjects into the high risk group (worse reclassification). The NRI offered by addition of “snoring duration” to the basic model was 0.4% (P = 0.925) (**Table 14**).

The basic model with “breathing pause” categorized 5.2% OSAS subjects into the high risk group (improved reclassification), and 0.9% non-OSAS subjects into the high risk group (worse reclassification). The NRI offered by addition of “breathing pause” to

the basic model was 4.2% (P = 0.31) (**Table 15**).

The basic model with “awaken” categorized 4.3% OSAS subjects into the high risk group (improved reclassification), and 0.9% non-OSAS subjects into the high risk group (worse reclassification). The NRI offered by addition of “awaken” to the basic model was 3.4% (P = 0.117) (**Table 16**).

4.4 Diagnostic ability of objective measures and/or subjective measures

The objective model includes objective measures significantly correlated with pediatric OSAS (i.e., tonsil hypertrophy, adenoid hypertrophy, and obesity). Of note, only subjective measures that significantly correlated with pediatric OSAS (i.e., snoring >5 nights/week, snoring >3month, breathing pause, and awaken) were used to add into the basic model. The combined model comprised both objective and subjective measures correlated with pediatric OSAS, that is, tonsil hypertrophy, adenoid hypertrophy, obesity, snoring >5 nights/week, snoring >3month, breathing pause, and awaken.

Table 17 listed diagnostic abilities comparing of the objective model, the subjective model, and the combined model for detecting pediatric OSAS. The likelihood ratio chi-square test was highly statistically significant for objective model, subjective model, and combined model (P <0.001). The C-index for objective model, subjective model, and combined model was 0.78, 0.72, and 0.84, respectively. **Figure 3** compared ROC curves between the objective model, subjective model, and the combined model. The Hosmer-Lemeshow test for the objective model, the subjective model, and the combined model showed adequate fit for models in detecting pediatric OSAS (P >0.05) (**Table 18**). **Figure 4** illustrated the calibration plots for the predictive model for the combined model (P = 0.626, Hosmer-Lemeshow test).

Table 19 listed comparisons of the difference in C-index between the objective model, the subjective model, and combined model. The difference in C-index significantly differed comparing the combined model with the objective model or subjective model (P = 0.0032 and P = 0.0001, respectively), indicating that combined model, as compared to the objective model or subjective model, had an increase in

discriminative properties. In addition, the difference in C-index did not significantly differ between objective model and subjective model (P = 0.2321), implying that the discriminative property was similar between these two models.

Table 20 shows IDI of subjective model on objective model and objective model on subjective model in detecting pediatric. By using the objective model, the mean predicted probability of OSAS was 0.636, and the mean predicted probability of OSAS was 0.398. The discrimination slope of the objective model between the OSAS and the non-OSAS subjects was 0.238. The discrimination slope of the objective model adding the subjective model was 0.342. The IDI for the objective model adding the subjective model was 10.4% (P <0.001).

By using the subjective model, the mean predicted probability of OSAS was 0.599, and the mean predicted probability of OSAS was 0.439. The discrimination slope of the subjective model between the OSAS and the non-OSAS subjects was 0.159. The discrimination slope of the subjective model adding the objective model was 0.342. The IDI for the subjective model adding the objective model was 18.2% (P <0.001).

Table 21 showed reclassification of OSAS risk comparing the subjective model with and without adding the objective model. The relevant strata for pediatric OSAS are categories as <50% (low risk) and >50% (high risk) predicted risk groups. The subjective model with “objective model” categorized 27.6% OSAS subjects into the high risk group (improved reclassification), and 5.7% non-OSAS subjects into the high risk group (worse reclassification). The NRI offered by addition of “objective model” to subjective model was 21.9% (P = 0.003), indicating that adding objective model to the subjective model significantly improved reclassification properties and resulted in 21.9% of subjects reclassified correctly in detecting OSAS.

Table 22 shows reclassification of OSAS risk comparing the objective model with and without adding “subjective model”. The relevant strata for detecting pediatric OSAS are categories as low risk (<50% OSAS risk) and high risk group (>50%). The objective model with “subjective model” categorized 11.2% OSAS subjects into the high risk group (improved reclassification), and 0.9% non-OSAS subjects into the high risk group (worse reclassification). Therefore, by addition of “subjective model” to the subjective model, the NRI was 10.3% (P = 0.044), indicating that adding subjective model to objective model also significantly improved reclassification properties and resulted in 10.3% of subjects reclassified correctly in detecting OSAS.

4.5 Validation

Leave-one-out cross-validation

Internal validation of the combined model was analyzed by the leave-one-out cross-validation. After cross-validation using the leave-one-out method, the C-index was 0.801 (**Table 23**). The result of internal validation showed no obvious ‘‘over-fitting’’ in the predictive discrimination between the OSAS and non-OSAS.

Bootstrap cross-validation

Internal validation of the combined model was analyzed by the bootstrapping method of 100, 200, and 500 iterations. By using the bootstrapping method for internal validation, the C-index was 0.812 at 100 iterations, 0.817 at 200 iterations, and 0.817 at 500 iterations (**Table 23**). The result of internal validation showed no obvious ‘‘over-fitting’’ in the predictive discrimination between the OSAS and non-OSAS.

K-fold cross-validation

Internal validation of the combined model was analyzed by the k-fold cross-validation. By using the k-fold method for internal validation, the C-index was 0.805 at 3 fold, 0.802 at 5 fold, and 0.804 at 10 fold (**Table 23**). The result of internal validation showed no obvious ‘‘over-fitting’’ in the predictive discrimination between the OSAS and non-OSAS.

5. Discussion

5.1 Objective measures and pediatric obstructive sleep apnea syndrome

Obesity, adenoid hypertrophy and tonsil enlargement play major roles in the pathophysiology of pediatric OSAS.[6,26] Also, objective measures for obesity and adnototonsillar size provide a guidance for the treatment. Adenotonsillectomy is widely considered to be the first-line therapy for pediatric OSAS,[41-46] while weight reduction is recommended in obese ones with OSAS. Previous studies examined correlations between adenotonsillar size and pediatric OSAS.[52-60] Nolan J *et al*.[52] systemically reviewed twenty articles comparing tonsil size to over-night polysomnogram, and showed an association between tonsil size and OSAS. Kang *et al*.[6] found the use of AN ratio for adenoid size measure is an easily applicable and non-invasive method in children and correlated well with pediatric OSAS. Obesity is an independent risk factor for OSAS in children.[5,29] Adipose tissue deposited around the pharynx and neck, along with hypertrophic adenoids and tonsils, largely contribute to obstructive sleep syndrome in obese children.[5,68] Consequently, this study used obesity, adenoid hypertrophy, and tonsil hypertrophy to build the objective model because of their major roles contributing to pediatric obstructive sleep disorders.

5.2 Subjective measures and pediatric obstructive sleep apnea syndrome

Snoring occurs in almost all children with SDB and is the main reason for caregivers to seek medical advices. Many reports observed high prevalence of snoring in children with OSAS as well as children with primary snoring.[8,9,11,14,90-97] Nieminen *et al*.[94] stated that half of the children or fewer with symptoms suggestive of OSAS actually had the condition. Consequently, snoring alone is an insensitive indicator of OSAS and it is difficult to make a diagnosis of OSAS based on a history of snoring alone.[14]

Numerous studies have assessed the accuracy of clinical symptoms and signs in detecting pediatric OSAS.[8,9,11,14,90-97] Brietzke *et al*.[8] systemically reviewed pertinent literatures and stated that snoring had a sensitivity of 44% to 97% and specificity of 4% to 58% in detecting pediatric OSAS. Besides, witness breathing pause had a sensitivity of 47% to 88% and specificity of 17% to 90%, whereas mouth breathing had a sensitivity of 29% to 78% and specificity of 27% to 46% in detecting pediatric OSAS.[8] In 2012, Certal *et al*.[9] conducted a meta-analysis for clinical assessment in detecting pediatric OSAS and concluded that tonsil size and snoring reported by caregivers had high sensitivity but low specificity, while excessive daytime somnolence, observed apnea, and difficulty in breathing during sleep had high specificity but low sensitivity in diagnosing OSAS. This study showed snoring frequency had a sensitivity of 77% with specificity of 48%, tonsil size had a sensitivity of 77% with specificity of 65%, and observed apnea had a sensitivity of 42% with specificity of 88% in detecting pediatric OSAS. These findings were consistent with precious study as snoring and tonsil size had high sensitivity but low specificity, while observed apnea had specificity but low sensitivity in detecting pediatric OSAS. Based on findings in this study, we also agree

with the consensus that neither single symptoms or signs have satisfactory performance in detecting pediatric OSAS. Therefore, combining several symptoms or signs to develop a diagnostic tool for pediatric OSAS is highly desired.

5.3 Combined measures in detecting pediatric obstructive sleep apnea syndrome

Many studies examined diagnostic abilities of a combination of subjective symptoms or questionnaires in detecting pediatric OSAS.[9,10,96,98-100] Brouilette *et al*.[96] suggested combined difficulty breathing during sleep, apnea observed by parents, and snoring to derived the “OSA score” to facilitate selection of children for treatment for OSAS. Chervin *et al*.[98] developed the “pediatric sleep questionnaire”, which was consist of scales from snoring, sleepiness, and behavior, and validated a reliable instrument to be used in clinical research when PSG is not feasible. Goldstein *et al*.[12,99] used a 15 items “clinical assessment score” correctly diagnosed 72% of referred children compared to overnight PSG. Spruyt *et al*.[100] developed the set of six hierarchically arranged questions with the area under the curve was 0.79 to aid the screening of children at risk for OSAS. This study combined symptoms of snoring frequency, snoring duration, awaken, and breathing pause for the subjective model and yielded the area under the curve was 0.72. Nevertheless, neither combined symptoms nor questionnaires have satisfactory performance in detecting pediatric OSAS. Therefore, alternative diagnostic models are needed to improve the accuracy.

Several recently studies combined subjective (e.g. symptoms or questionnaires) and objective (e.g. physical examinations or radiological findings) measures in detecting pediatric OSAS.[9-11,13,99] Xu et al.[11] asserted combining clinical and radiologic findings might be helpful in detecting pediatric OSAS. Yang *et al*.[101] screened children for OSAS based on questionnaire, physical examination and electronic nasopharyngoscopy. Villa *et al*.[13] used the “sleep clinical record” consist of physical examination, subjective symptoms, and clinical history, to screen patients as candidates for PSG study. Although

combining subjective and objective measures have been used repeatedly for pediatric OSAS screening in precious literatures, none of them compared diagnostic abilities between objective and subjective measures. By using traditional and novel statistical methods, this study provides a comprehensive view of models based on objective and subjective measures. This study further confirmed the usefulness and feasibility to combine both objective and subjective measures for screening pediatric OSAS. Based on our findings, physicians should utilize a combined objective and subjective measures when developing a screen tool for pediatric OSAS to optimize its diagnostic abilities.

5.4 Strength and Limitations

To our best knowledge, the present study is the first study elaborating diagnostic abilities of objective measures, subjective measures, and combined objective and subjective measures in detecting pediatric OSAS. This study demonstrated that combined objective and subjective measures, as compared to objective measures or subjective measures, provide incremental value for disease discrimination and reclassification. From a clinical perspective, these findings warrant the need of use both objective and subjective measures in developing a screen tool for pediatric OSAS in order to optimize the diagnostic abilities of the tool.

The strength of this study is the application of a variety of statistical method for this important topic in pediatric sleep medicine. We used global model fit, discrimination (C index), calibration (Hosmer-Lemeshow goodness-of-fit statistic), and reclassification statistics for assessing diagnostic abilities of clinical measures in pediatric population. Specifically, the ability to reclassify risk, as showed in this study, offers increases in clinical utility of diagnostic tool to detect pediatric OSAS. The validation process is also worthy to mention. We applied three different statistical methods for internal validation and all showed fair performance of the model. Furthermore, this study comprises a large sample size, which is well representative of pediatric population and allow clinicians to have a comprehensive understanding of obstructive sleep disorders in children.

This study has certain limitations. First, this study was conducted in a single, tertiary referral medical center. Therefore, cross-cultural and racial differences of clinical measures in children with obstructive sleep disorders were not obtained. Second, this study did not examine nasal or tongue base conditions, although correlations between

nasal or tongue base structure and OSAS have not been well established in pediatric population.[102] Third, objective measures in this study only reflect the upper airway structure in two dimensions. Three-dimensional imaging, including computed tomography or magnetic resonance imaging, although high cost and thus not routinely used, may be more accurate for upper airway evaluations.[103,104] Fourth, our patients were recruited from clinics, which were located in a tertiary medical referral center rather than from the community. The associations between objective or subjective measures and pediatric OSAS in normal populations require further study.

5.5 Future Perspectives

Pediatric OSAS is an upper airway disorders. This study elucidated correlations between objective measures and pediatric OSAS. However, objective measures included in this study were mainly 2-dimentional. Recently, cone beam computed tomography (CBCT) emerged as a useful tool in diagnosis and treatment planning of maxillofacial diseases.[104] It may also offer more detailed assessment of 3-dimentional upper airway structures than traditional 2-dimentional measures does in assessing airway patency of children with SDB. In the future, we will conduct a prospective study investigating relationships between pediatric SDB and upper airway patency determined by CBCT.

Untreated OSAS in children is associated with adverse cardiovascular consequences. Also, child obesity increases the risk of OSAS.[3] Obesity is associated with alterations in endocrine and inflammatory process of fat cells, many of which may modulate blood pressure and respiratory control.[2,3] Nowadays, Childhood obesity is increasingly recognized to be associated with both pediatric OSAS and hypertension.[2,3] As obesity related OSAS is highly prevalent, more research is needed to understand the interaction of these two conditions with its connections to adverse cardiovascular events. In the future, we will conduct prospective studies to further clarify associations between obesity, pediatric OSAS, and adverse cardiovascular consequences.

6. Conclusion

Combined objective and subjective measures, as compared with objective measures or subjective measures, provide incremental value of disease discrimination for pediatric OSAS. Furthermore, detecting subjects with OSAS by a combination of objective and subjective measures significantly reclassified children more accurately than by objective or subjective measures alone. Based on these findings, clinicians should consider using both objective and subjective measures in developing a screen tool for pediatric OSAS to optimize the diagnostic abilities.

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8. Figures

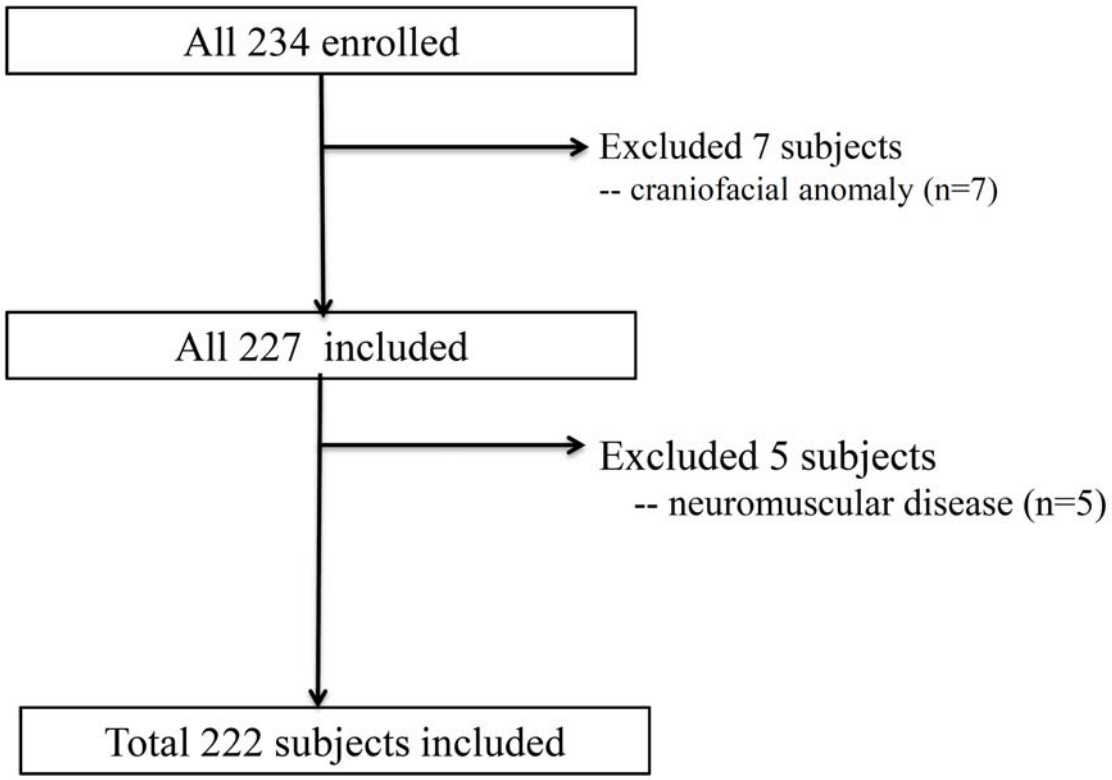

Figure 1 Flow diagram for included and excluded subjects

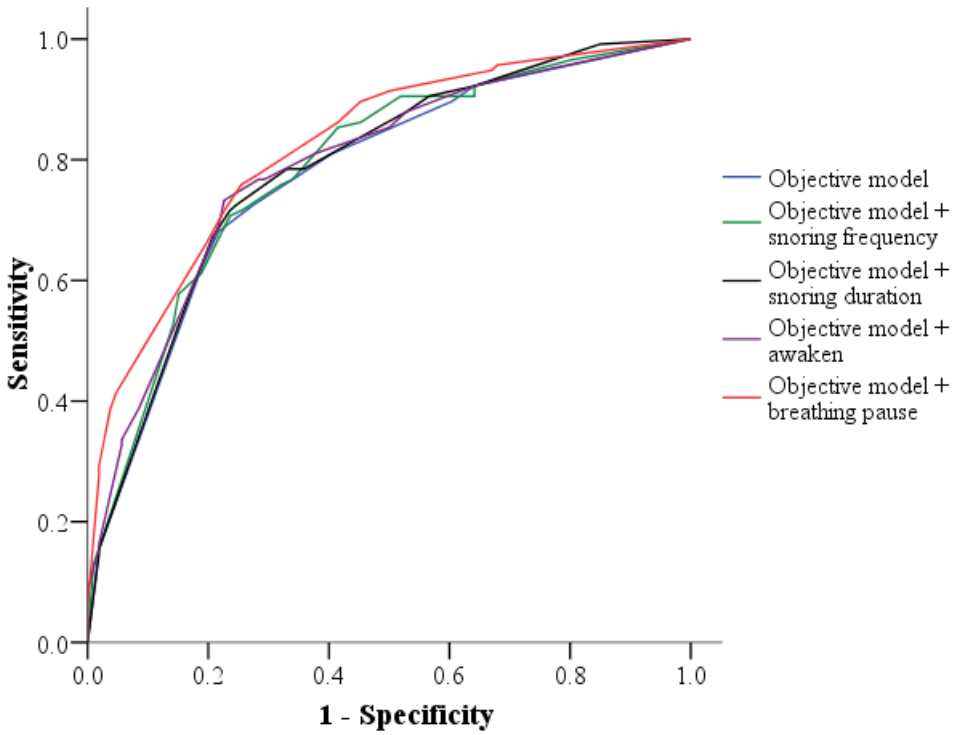

Figure 2 Receiver operating characteristics of the objective model with one subjective measure

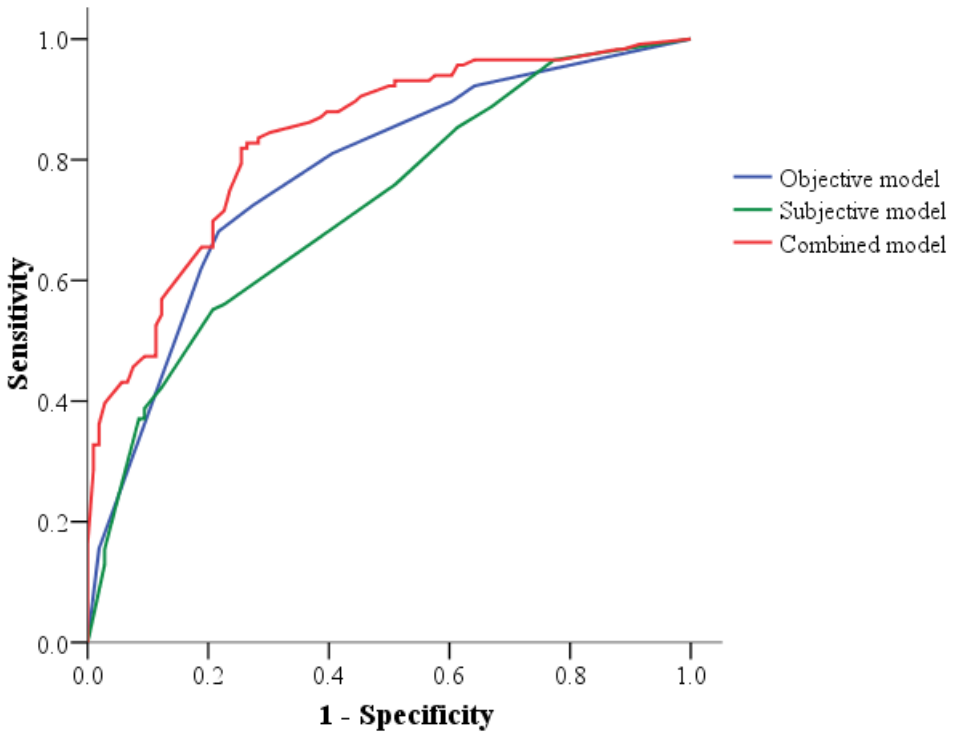

Figure 3 Receiver operating characteristics comparing the objective model, subjective model, and the combined model

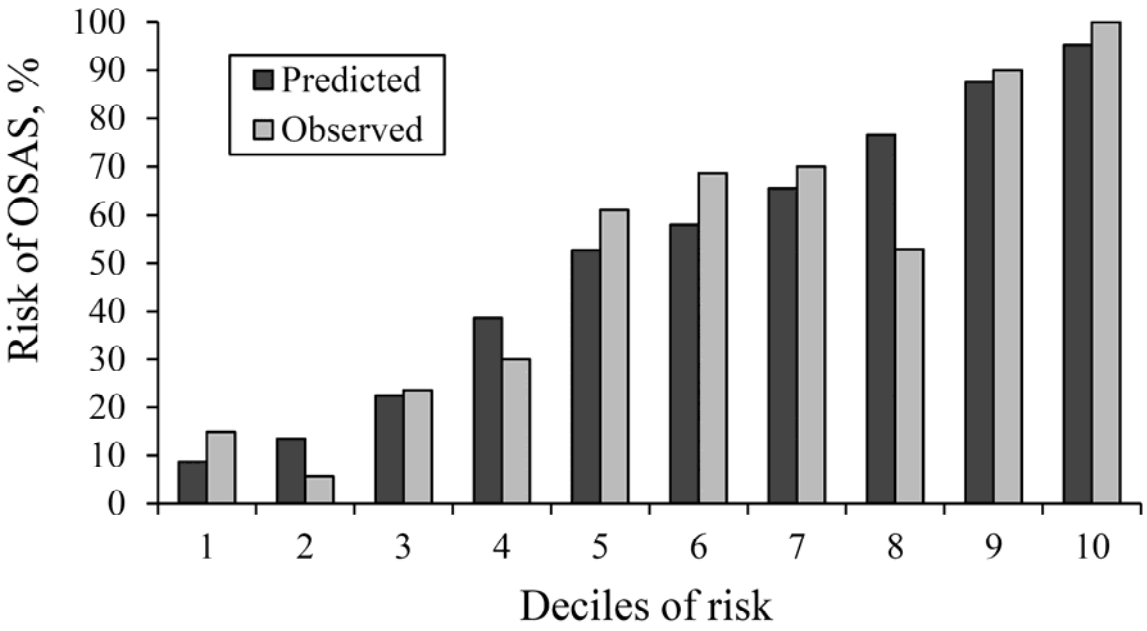

Figure 4 Calibration plots for the predictive model for the combined model (P = 0.626, Hosmer-Lemeshow test)

9. Tables

Table 1 Characteristics in all participants (N=222)

	N	%
Gender		
Male	149	67.1
Female	73	32.9
Adiposity		
Obese	48	21.6
Non-obese	174	78.4
Adenoid hypertrophy	134	60.4
Tonsil hypertrophy	126	56.8
Tonsil size		
Grade 1	14	6.3
Grade 2	82	36.9
Grade 3	82	36.9
Grade 4	44	19.8
Disease severity		
AHI <1	106	47.7
AHI ≥ 1	116	52.3

Note: AHI = apnea /hypopnea index.

Table 2 Demographic data and sleep studies in all participants (N=222)

	Mean ±SD	Min-Max	Q1	Q2	Q3
Age, year	7.3 ± 3.7	1.4-17.8	4.7	6.5	9.4
Weight, kg	29.2 ± 16.2	10-93	18.0	22.9	34.7
Height, cm	122.2 ± 21.7	79-185	106.8	119.5	136.3
BMI, kg/m^2	18.1 ± 3.9	11.4-31.2	15.3	16.8	20.4
BMI percentile	62.2 ± 30.7	2-99	37.8	64.7	92.3
AN ratio	0.69 ± 0.16	0.30-0.95	0.58	0.73	0.83
AHI, event/hour	5.4 ± 13.0	0-130.5	0.3	1.0	3.4
MeanSaO_2, %	97.2 ± 2.2	70.0-99.4	97	97.7	98
MinSaO_2, %	88.8 ± 2.2	50-97	86	91	93

Note: AHI = apnea /hypopnea index; AN ratio = adenoidal-nasopharyngeal ratio; BMI = body mass index; SaO_2 = oxygen saturation.

Table 3 Objective and subjective measures in all participants (N=222)

	N	%
Objective measure		
Tonsil hypertrophy	126	56.8
Adenoid hypertrophy	134	60.4
Obesity	48	21.6
Subjective measure		
Snoring > 5 nights/week	144	64.9
Snoring > 3month	166	74.8
Diaphoresis	53	23.9
Awaken	71	32.0
Bedwetting	27	12.2
Nightmare	60	27.0
Breathing pause	62	27.9
Nasal speech	178	80.2
Mouth breathing	179	80.6
Weight gain	38	17.1
Weight loss	14	6.3
Sleepiness	35	15.8
Attention	93	41.9
Depression	3	1.4
Low self-esteem	18	8.1
Shy	31	14.0
Hyperactive	50	22.5
Low academic performance	39	17.6

Table 4 Correlation between age (in year) and adenotonsillar size stratified by OSAS

	Tonsil		Adenoid	
Subgroup	ρ†	*P*	ρ†	*P*
AHI＜1	-0.10	0.300	-0.56	< 0.001
AHI ≥1	-0.17	0.062	-0.55	< 0.001

† Spearman rank correlation

Table 5 Comparison of adenotonsillar size among age groups stratified by OSAS

	Toddler (12 month to 3 years)	Preschool (3 years to 6 years)	School (6 years to 12 years)	Adolescence (12 years to 18 years)	*P* trend†
Tonsil grade					
AHI＜1	2.3 (0.8)	2.3 (0.6)	2.4 (0.8)	2.0 (0.7)	0.612
AHI ≥1	3.3 (0.7)	3.0 (0.8)	3.2 (0.7)	2.6 (0.9)	0.086
Adenoid					
AHI＜1	0.80 (0.06)	0.68 (0.13)	0.63 (0.16)	0.47 (0.11)	< 0.001
AHI ≥1	0.79 (0.07)	0.81 (0.07)	0.72 (0.16)	0.57 (0.12)	< 0.001

† Kruskal-Wallis test

Table 6 Comparisons of demographics between OSAS and non-OSAS children

	OSAS (n = 116)	Non-OSAS (n = 106)	P
Gender			0.270
Male	74 (63.8)	75 (70.8)	
Female	42 (36.2)	31 (29.2)	
Age, year	7.6 ± 4.0	7.1 ± 3.2	0.355
Weight, kg	31.5 ± 18.9	26.8 ± 12.4	0.031*
Height, cm	123.0 ± 23.3	121.3 ± 19.9	0.543
BMI, kg/m^2	18.9 ± 4.6	17.3 ± 2.8	0.002*
BMI percentile	64.9 ± 31.0	59.3 ± 30.3	0.175
AHI, event/hour	9.9 ± 16.8	0.4 ± 0.3	<0.001*
MeanSaO_2, %	96.6 ± 2.8	97.7 ± 0.9	<0.001*
MinSaO_2, %	86.1 ± 6.8	91.7 ± 3.4	<0.001*

Note: AHI = apnea /hypopnea index; BMI = body mass index; SaO_2 = oxygen saturation

* indicates that the significant level was below 0.05.

Table 7 Clinical measures in detecting pediatric OSAS (AHI ≥1 as OSAS).

	OSAS (*n* = 116)	Non-OSAS (*n* = 106)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P*	OR (95% CI)
Objective measure								
Female gender	36.2%	29.2%	29.2	63.8	42.5	49.7	0.271	1.4 (0.8–2.4)
Age <6 years	44.0%	39.6%	39.6	56.0	45.2	50.4	0.513	1.2 (0.7–2.0)
Tonsil hypertrophy	76.7%	34.9%	76.7	65.1	70.6	71.9	<0.001*	6.1 (3.4–11.1)
Adenoid hypertrophy	75.0%	44.3%	75.0	55.7	64.9	67.0	<0.001*	3.8 (2.1–6.7)
Obesity	28.4%	14.2%	28.4	85.8	68.8	52.3	0.01*	2.4 (1.2–4.8)
Subjective measure								
Snoring > 5 nights/week	76.7%	51.9%	76.7	48.1	61.8	65.4	<0.001*	3.1 (1.7–5.4)
Snoring > 3month	83.6%	65.1%	83.6	34.9	58.4	66.1	0.002*	2.7 (1.5–5.2)
Diaphoresis	24.1%	23.6%	24.1	76.4	52.8	47.9	0.923	1.0 (0.6–1.9)
Bedwetting	14.7%	9.4%	14.7	90.6	63.0	49.2	0.238	1.6 (0.7–3.8)
Awaken	35.7%	25.0%	35.7	75.0	63.5	48.8	0.04*	1.7 (1.0–2.7)
Nightmare	26.7%	27.4%	26.7	72.6	51.7	47.5	0.915	1.0 (0.5–1.8)
Breathing pause	42.2%	12.3%	42.2	87.7	79.0	58.1	<0.001*	5.2 (2.6–10.4)
Nasal speech	78.4%	82.1%	78.4	17.9	51.1	43.2	0.499	0.8 (0.4–1.5)
Mouth breathing	83.6%	77.4%	83.6	22.6	54.2	55.8	0.240	1.5 (0.8–2.9)
Sleepiness	19.0%	12.3%	19.0	87.7	62.9	49.7	0.174	1.7 (0.8–3.5)
Attention	41.4%	42.5%	41.4	57.5	51.6	47.3	0.871	1.0 (0.6–1.6)
Depression	0.9%	1.9%	0.9	98.1	33.3	47.5	0.519	0.5 (0.0–5.1)
Low self-esteem	6.9%	9.4%	6.9	90.6	44.4	47.1	0.491	0.7 (0.3–1.9)
Shy	14.7%	13.2%	14.7	86.8	54.8	48.2	0.756	1.1 (0.5–2.4)
Hyperactive	20.7%	24.5%	20.7	75.5	48.0	46.5	0.494	0.8 (0.4–1.5)
Low academic performance	19.0%	16.0%	19.0	84.0	56.4	48.6	0.567	1.2 (0.6–2.5)

Note: Data were analyzed using Chi-square test. CI = confidence internal; NPV = negative predictive value; OR = odds ratio; OSAS = obstructive sleep apnea syndrome; PPV = positive predictive value. * indicates that the significant level was below 0.05.

Table 8 Multiple logistic regression model of measures in detecting pediatric OSAS

	B	*P*	OR (95% CI)
Tonsil hypertrophy	1.98	<0.001*	7.2 (3.5–14.8)
Adenoid hypertrophy	0.69	0.047*	2.0 (1.0–3.9)
Obesity	0.76	0.068	2.1 (0.9–4.8)
Snoring > 5 nights/week	0.33	0.382	1.4 (0.7–2.9)
Snoring > 3month	0.30	0.475	1.3 (0.6–3.1)
Awaken	0.75	0.043*	2.1 (1.0–4.4)
Breathing pause	1.74	<0.001*	5.7 (2.4–13.5)

Note: OSAS = obstructive sleep apnea syndrome; OR = odds ratio.

* indicates that the significant level was below 0.05.

Table 9 Collinearity diagnostics of the seven clinical measures in detecting pediatric OSAS

	Tolerance	Variance inflation factor
Tonsil hypertrophy	0.89	1.13
Adenoid hypertrophy	0.85	1.17
Obesity	0.96	1.04
Snoring >5 nights/week	0.77	1.29
Snoring >3month	0.81	1.24
Awaken	0.98	1.02
Breathing pause	0.87	1.15

Note: OSAS = obstructive sleep apnea syndrome.

Table 10 Global model fit when adding each subjective measure on objective model in detecting pediatric OSAS

Model	Likelihood Ratio Chi-Square	P Value of Chi-Square	Nagelkerke R^2	Akaike Information Criterion	Bayes Information Criterion
Objective model	56.7	<0.001	30.1	36.4	50.0
+ snoring frequency	62.4	<0.001	32.7	66.0	83.0
+ snoring duration	61.6	<0.001	32.3	52.8	69.8
+ awaken	61.7	<0.001	32.4	55.8	72.8
+ breathing pause	80.7	<0.001	40.7	48.2	65.2

Note: Objective model = adenoid hypertrophy + tonsil hypertrophy + obesity.

OSAS = obstructive sleep apnea syndrome.

Table 11 Discrimination and calibration properties when adding each subjective measure on objective model in detecting pediatric OSAS

Model	C-Index	△C-Index	P Value for △ C-Index	Chi-Square for HL†	P Value of HL
Objective model	0.775	–	–	2.0	0.848
+ snoring frequency	0.788	0.013	0.191	3.9	0.793
+ snoring duration	0.786	0.011	0.163	4.2	0.753
+ awaken	0.790	0.015	0.185	6.5	0.480
+ breathing pause	0.822	0.047	0.001	0.73	0.994

Note: † HL = Hosmer–Lemeshow statistic using deciles of risk for OSAS probabilities.

Objective model = adenoid hypertrophy + tonsil hypertrophy + obesity.

OSAS = obstructive sleep apnea syndrome.

Table 12 Integrated discrimination improvement of each subjective measure on objective model in detecting pediatric OSAS

Model	Predicted probability of OSAS	Predicted probability of non-OSAS	Discrimination slope	IDI (%)†	*Z* Value for IDI†	*P* Value for IDI†
Objective	0.636	0.398	0.238	—	—	—
+ snoring frequency	0.646	0.387	0.259	2.1%	2.18	0.029
+ snoring duration	0.644	0.389	0.255	1.7%	1.87	0.062
+ awaken	0.644	0.389	0.255	1.7%	1.97	0.048
+ breathing pause	0.675	0.355	0.320	8.2%	4.47	<0.001

† Compare to objective model; IDI = integrated discrimination improvement.

Table 13 Reclassification table for predicted pediatric OSAS risk using objective measures with and without adding “snoring frequency”

	Number of subjects		Reclassified		Net Correctly Reclassified, %
	＜50%	≥ 50%	Increased Risk	Decreased Risk	
	Predicted OSAS risk with "snoring frequency"				
Subjects with OSAS (*n* = 116)					
Predicted OSAS risk without "snoring frequency"					
＜50%	27	5	5	1	3.4%
≥ 50%	1	83			
Subjects without OSAS (*n* = 106)					
Predicted OSAS risk without "snoring frequency"					
＜50%	70	7	7	2	-4.7%
≥ 50%	2	27			
Net reclassification improvement, %					-1.3%
P value					N.A.

Note: OSAS = obstructive sleep apnea syndrome.

Table 14 Reclassification table for predicted pediatric OSAS risk using objective measures with and without adding “snoring duration”

	Number of subjects		Reclassified		Net Correctly Reclassified, %
	＜50%	≥50%	Increased Risk	Decreased Risk	
	Predicted OSAS risk with "snoring duration"				
Subjects with OSAS (*n* = 116)					
Predicted OSAS risk without "snoring duration"					
＜50%	25	7	7	0	6.0%
≥50%	0	84			
Subjects without OSAS (*n* = 106)					
Predicted OSAS risk without "snoring duration"					
＜50%	68	9	9	3	-5.7%
≥ 50%	3	26			
Net reclassification improvement, %					0.4%
P value					0.925

Note: OSAS = obstructive sleep apnea syndrome.

Table 15 Reclassification table for predicted pediatric OSAS risk using objective measures with and without adding “breathing pause”

	Number of subjects		Reclassified		Net Correctly Reclassified, %
	＜50%	≥50%	Increased Risk	Decreased Risk	
	Predicted OSAS risk with "breathing pause"				
Subjects with OSAS (*n* = 116)					
Predicted OSAS risk without "breathing pause"					
＜50%	24	8	8	2	5.2%
≥50%	2	82			
Subjects without OSAS (*n* = 106)					
Predicted OSAS risk without "breathing pause"					
＜50%	71	6	6	5	-0.9%
≥ 50%	5	24			
Net reclassification improvement, %					4.2%
P value					0.308

Note: OSAS = obstructive sleep apnea syndrome.

Table 16 Reclassification table for predicted pediatric OSAS risk using objective measures with and without adding “awaken”

	Number of subjects		Reclassified		Net Correctly Reclassified, %
	＜50%	≥50%	Increased Risk	Decreased Risk	
	Predicted OSAS risk with "awaken"				
Subjects with OSAS (*n* = 116)					
Predicted OSAS risk without "awaken"					
＜50%	27	5	5	0	4.3%
≥50%	0	84			
Subjects without OSAS (*n* = 106)					
Predicted OSAS risk without "awaken"					
＜50%	76	1	1	0	-0.9%
≥ 50%	0	29			
Net reclassification improvement, %					3.4%
P value					0.117

Note: OSAS = obstructive sleep apnea syndrome.

Table 17 Global model fit comparing subjective model, objective model, and combined model in detecting pediatric OSAS

Model	Likelihood Ratio Chi-Square	P Value of Chi-Square	Nagelkerke R^2	Akaike Information Criterion	Bayes Information Criterion
Objective model	56.7	<0.001	30.1	36.4	50.0
Subjective model	37.8	<0.001	20.9	54.1	71.1
Combined model	87.1	<0.001	43.3	133.6	160.8

Note: OSAS = obstructive sleep apnea syndrome.

Objective model = adenoid hypertrophy + tonsil hypertrophy + obesity.

Subjective model = snoring frequency + snoring duration + breathing pause + awaken.

Table 18 Discrimination and calibration properties comparing subjective model, objective model, and combined model in detecting pediatric OSAS

Model	C-Index	Chi-Square for HL†	P Value of HL
Objective model	0.78	2.01	0.848
Subjective model	0.72	4.42	0.730
Combined model	0.84	6.19	0.626

Note: † HL = Hosmer–Lemeshow statistic using deciles of risk for OSAS probabilities.

Objective model = adenoid hypertrophy + tonsil hypertrophy + obesity.

Subjective model = snoring frequency + snoring duration + breathing pause + awaken.

OSAS = obstructive sleep apnea syndrome.

Table 19 Comparison of discrimination properties of pediatric OSASA among different models

Contrast	ΔAUC	SE	95% CI of ΔAUC	P
Objective *vs*. Subjective	0.0531	0.0444	-0.0340 to 0.140	0.2321
Objective *vs*. Combined	0.0610	0.0207	0.0205 to 0.101	0.0032*
Subjective *vs*. Combined	0.114	0.0289	0.0574 to 0.171	0.0001*

Note: AUC = area under the ROC curve; SE = standard error; CI = confidence interval.

* indicates that the significant level was below 0.05.

Table 20 Integrated discrimination improvement of subjective model on objective model and objective model on subjective model in detecting pediatric OSAS

Model	Predicted probability of OSAS	Predicted probability of non-OSAS	Discrimination slope	IDI (%)†	*Z* Value for IDI†	*P* Value for IDI†
Objective	0.636	0.398	0.238	—	—	—
Subjective	0.599	0.439	0.159	—	—	—
Combined (vs. objective)	0.686	0.344	0.342	10.4%	5.01	<0.001
Combined (vs. subjective)	0.686	0.344	0.342	18.2%	6.93	<0.001

† Compare to objective model;

IDI = integrated discrimination improvement.

Table 21 Reclassification table for predicted pediatric OSAS risk using subjective measures with and without adding objective measures

	No. of subjects		Reclassified		Net
			Increased	Decreased	Correctly
	＜50%	≥50%	Risk	Risk	Reclassified, %
	Predicted OSAS risk with "objective measures"				
Subjects with OSAS (*n* = 116)					
Predicted OSAS risk without "objective measures"					
＜50%	15	36	36	4	27.6%
≥50%	4	61			
Subjects without OSAS (*n* = 106)					
Predicted OSAS risk without "objective measures"					
＜50%	66	16	16	10	-5.7%
≥ 50%	10	14			
Net reclassification improvement, %					21.9%
P value					0.003

Note: OSAS = obstructive sleep apnea syndrome.

Table 22 Reclassification table for predicted pediatric OSAS risk using objective measures with and without adding subjective measures

	No. of subjects		Reclassified		Net
			Increased Risk	Decreased Risk	Correctly Reclassified, %
	＜50%	≥50%			
	Predicted OSAS risk with "subjective measures"				
Subjects with OSAS (*n* = 116)					
Predicted OSAS risk without "subjective measures"					
＜50%	17	15	15	2	11.2%
≥50%	2	82			
Subjects without OSAS (*n* = 106)					
Predicted OSAS risk without "subjective measures"					
＜50%	69	8	8	7	-0.9%
≥ 50%	7	22			
Net reclassification improvement, %					10.3%
P value					0.044

Note: OSAS = obstructive sleep apnea syndrome.

Table 23 Validation statistics of the combined model

	Leave-one-out	Bootstrap			K-fold		
		100 iterations	200 iterations	500 iterations	K=3	K=5	K=10
C-index	0.801	0.812	0.817	0.817	0.805	0.802	0.804