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■期中進度報告

（計畫名稱）

依序利用 Oximeter 診斷重度及 PSG 診斷輕、中度阻塞性睡眠缺氧症以降低醫療成本

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計畫主持人：陳永福
共同主持人：杭良文、林妍如、林宣宏
計畫參與人員：廖怡岑、黃春森

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中文摘要

阻塞性睡眠呼吸中止症（OSA）是導致慢性病的重要原因，包括代謝症候群、慢性過度換氣症候群、上胸呼吸型疾病、氣管發炎、阻塞性肺部疾病、神經肌肉症、小兒麻痺、肥胖症、心衰竭、顱顏異常、人格改變、智力異常、認知不足、體力改變、注意力衰弱或勃起功能異常等。它也是造成車禍的重要原因，先前的研究顯示，罹患 OSA 之病人較正常人之車禍發生率提高 2～7 倍。

睡眠多項生理檢查（PSG）是一項複雜的診斷檢查，它可以在受測者睡眠時測量及記載多個生理變項，其中，第一型 PSG 被視為診斷阻塞性睡眠呼吸中止症（OSA）的黃金標準。但是其缺點為檢查人力需求大、費時、價格昂貴。本研究之動機為：(1)根據先前的研究報告顯示，即使在已開發國家（例如歐洲、澳洲、美國、加拿大），等候 PSG 檢查之時間很長；(2)簡單便宜的家庭式診斷工具結合問卷可以有效預測嚴重的 OSA 患者；(3)利用支援向量機等人工智慧技術來設計臨床診斷支援系統可以提昇診斷之正確率。本計畫之目的為經由問卷及簡單儀器(血氧機診斷)獲得之參數,利用人工智慧技術設計臨床診斷支援(CDS)系統來有效診斷嚴重之 OSA 病人，馬上進行治療。本計畫之目標為：(1)臨床檢驗家測式血氧機(oximeter)診斷 OSA 病人之效率；(2)研究病患在睡眠實驗室之實際睡眠時間為多久時才具有診斷價值；(3)利用支援向量機(support vector machine)來設計 CDS 系統診斷 OSA 病人；(4)分析目前健保體制下，首先以血氧機診斷重症 OSA 病患，然後再以 PSA 診斷正常、輕度、中度 OSA 病患過程中之成本效益。

本研究共收集 699 個疑似 OSA 病例，利用 PSG 進行睡眠檢查，去除 20 歲以下及 85 歲以上之病例後剩下 651 個病例，另外如果移除睡眠不足 4 小時之病例後，只剩下 561 筆資料供後續分析。經由統計分析及參數篩選之後利用 SVM 進行預測模型之建構，進行重度病人(AHI>30)或中度以上病人(AHI>15)之偵測。初步研究結果顯示，以所設計之 CDS 系統雛型，利用氧氣未飽和指數(Oxygen Desaturation Index, ODI)變數作為診斷參數時，診斷重症病患 (準確率：89.04%、靈敏度：94.52%、專一度：82.36%)及中度以上病人(準確率：87.05%、靈敏度：88.57%、專一度：86.25%)之診斷效率佳。此結果(靈敏度/專一度)比最近所發表之結果（重症：87.8%/96.6%、中度以上：84.0%%/84.4%%）之效能更好。初步之成本效益分析顯示，在目前台灣之健保付費制度下，利用本研究所提出的方法，平均每一病例成本可以降低台幣 1577 元 (34.58%) 之成本。

關鍵詞: 阻塞性睡眠呼吸中止症、血氧濃度計、支援向量機器、基因演算法、睡眠多項生理檢查(PSG)、成本效益分析。

Abstract

Obstructive sleep apnea (OSA) is a significant cause of motor vehicle crashes and chronic diseases. Polysomnography (PSG) has been widely applied in the diagnosis of OSA that a number of physiologic variables are measured and recorded during sleep. Although PSG is treated as the gold standard for diagnosing OSA, it is labor-intensive, time-consuming, and expensive. Therefore, clinical diagnosis of high-risk OSA patients using questionnaires and cheap home diagnostic devices has a great potential in reducing healthcare cost and in eliminating insomnia caused by environmental variation for some patients when tested in the sleeping center.

A total of 699 patients with possible OSA had been recruited and tested using PSG for overnight attending at the Sleep Center of China Medical University Hospital from Jan. 2004 to Dec. 2005. Subjects with age less than 20 or more than 85 years old were excluded, only 651 patient data were used for analysis. Furthermore, by removing data collected from patients with sleeping time less than 4 hours, only the data of 561 patients were used for further analysis. After statistical analysis and feature selection, a model constructed based on support vector machine (SVM) was then used to discriminate severe (AHI>30) or severe and moderate (AHI>15) patients from other subjects. The results show that oxyhemoglobin desaturation index (ODI) alone provide satisfactory diagnostic performance in diagnosing severe OSA patients (accuracy: 89.04%, sensitivity: 94.52%, specificity: 82.36%) and combined severe and moderate OSA patients (accuracy: 87.05%, sensitivity: 88.57%, specificity: 86.25%). Based on the cost-benefit analysis, we suggest that home-styled oximeter can be used to sift severe patients from all suspected patients at the first stage, which is then followed by the PSG examination for discriminating normal subjects and mild and moderate patients. It was found that an average cost reduction of NT$1577 (34.58%) per case can be achieved under the current Taiwanese insurance setting.

Keywords: Obstructive sleep apnea (OSA), Oximetry, Support Vector Machine (SVM), Polysomnography (PSG), Cost-benefit analysis

1. Introduction

Sleep disorder is a spectrum of diseases which include snoring, upper airway resistance syndrome and obstructive sleep apnea (OSA) (Pang et al. 2006). It highly linked to hypertension due to sleep fragmentation, intermittent hypoxemia, and increased sympathetic tone. Snoring has strong relationship with daytime sleepiness (80%), obesity (73%), and chronic fatigue (78%) (Hunsaker et al. 2006). Obstructive sleep apnea (OSA) is a common sleep disorder and is commonly seen in 24% of men and 9% of women (Young et al. 1993). Among them, up to 93% of women and 82% of men have not been diagnosed (Young et al. 1997). Furthermore, OSA is a significant cause of motor vehicle crashes resulting in an increased risk of 2-7 folds (N. Hartenbaum et al. 2006) and causes of several chronic diseases. For example, OSA was found to closely relate to metabolic syndrome, an established cardiovascular risk factor, in middle-aged subjects (Lam et al. 2006); chronic hyperventilation syndrome and upper chest breathing pattern disorders (Coffee 2006); bronchial inflammation (Devouassoux et al. 2007); obstructive pulmonary disease, neuromuscular disease, poliomyelitis, obesity, cardiovascular disease, and cranio-facial anomalies (Coffee 2006, Taman and Gozal 2006); personality change and intellectual impairment (Montplaisir et al. 1992); cognitive deficits, vigilance alteration and attentional decline (Gosselin et al. 2006); and erectile dysfunction (Teloken et al. 2006).

Polysomnography (PSG) is treated as the gold standard for detecting Patients with OSA (Chesson et al. 2003, Flemons et al 2003). It is a diagnostic test during which a number of physiologic variables are measured and recorded during sleep. Currently, PSG monitors can be classified into four different types based on the number of channels used to record biological signals, in which Type 1 monitor is in-laboratory, overnight, and technician-attended polysomnograph that has been used as the reference standard to which other types of monitors are compared (Flemons et al. 2003). In contrast, Type 2 monitor is a comprehensive portable polysomonogram (PSG) that a minimum of 7 channels, such as electroencephalograph (EEG), elctrooculograph (EOG), chin electromyography (EMG), electrocardiograph (ECG) for measuring heart rate, airflow, inductance plethysmorgraphy for recording respiratory effort, and

oximetry for measuring arterial oxygen saturation, are used to record the bio-signals. On the other hand, Type 3 is a modified portable sleep apnea testing consists of a minimum of 4 channels including ventilation or airflow (2 channels), ECG or heart rate, and Oxyhemoglobin saturation. In contrast, Type 4 PSG is applied to continuously record only one or two biological parameters and has the potential to be used at home as a cheap diagnostic device for diagnosing OSA patients.

Prediction of OSA using questionnaires, demographics, clinical features, and physiological examination has been extensively studied in the last decade (Goncalves et al. 2004, Dixon et al. 2003, Pang et al. 2006). Goncalves et al. (2004) used Epworth sleeping scale (ESS), the sleeping disorders questionnaire, the Beck depression inventory (BDI), the medical outcome study 36-item short form health survey (SF-36), and a questionnaire on driving difficulties and accidents to evaluate subjects who were suspected to have sleep-disordered breathing (SDB) or obstructive sleep apnea. Among them, ESS was found to be correlated to arousal index and AHI (Goncalves et al. 2004), which contradicted to the investigations done by Pang et al. (2006) and Dixon et al. (2003). Khoo et al. (2004) used questionnaires, containing questions regarding snoring, choking, suffocating, and abrupt awaking during sleep, to study Asian populations including Chinese, Malaysian, and Indian. It was found that the risk factors are similar to white populations in strong association of snoring and sleep apnea with male gender, older age, obesity, family history, and smoking. In addition, demographic, clinical, and biochemical factors including age, sex, observed sleep apnea, fasting insulin, glycosylated hemoglobin A_{IC}, and central (waist circumference, BMI) and upper body (neck circumference) obesity were found to significantly increase the risk of higher AHI for the severely obese patients (Dixon et al. 2003). Strong correlation between patient self-perception and clinical examination, including Friedman tongue position grade and Friedman clinical staging, of OSA severity and AHI was also found (Pang et al. 2006).

Although PSG is treated as the gold standard, it, however, is time-consuming, labor-intensive, and expensive (Pang et al. 2006). According to a recent report, waiting time for accessing to diagnosis and treatment of patients with suspected OSA is lengthy even in the developed counties

around Europe, Australia, the United States, and Canada. For example, it was estimated that the waiting time for non-urgent referrals for a sleep study ranges from 0 to 48 months in UK, 2 weeks to 2 months in Belgium, 4 to 68 weeks in Australia, a few weeks to more than a year in the US, and 8 to 30 months in Canada (Flemons et al. 2004). In Taiwan, the waiting time is between 1 to 7 months depending on which hospitals the patients have been referred. For example, the average waiting time of an academic hospital located in central Taiwan area is around 2 months based on the information provided by the co-advisor (Dr. Hang). Hence, other devices which are cheap, safe, and accurate; readily and easily accessed; and have no risk or side effect to the patients are valuable and needed for decreasing waiting time and cost for OSA diagnosis (Pang et al. 2006).

In addition to labor-intensive, time-consuming, and high examination cost, PSG also has other limitations, such as technical expertise required and timely access restricted (Flemons et al. 2003). Thus, several alternative and simpler diagnostic devices have been evaluated. Home pulse oximeter has been proposed as a valuable screening tool, although its effectiveness in screening patients with OSA has been debated for several years (Netzer et al. 2001). Several studies have assessed its usefulness, but sometimes with conflicting results (Choi et al 2000, Shinji et al. 2002, Juan-Carlos et al. 2000). For example, home overnight oximetry was found to be not very correlated with PSG for testing children (Kirk et al. 2003) and to be inconsistent with night-to-night variability for aged patients with chronic obstructive pulmonary disease (COPD) (Lewis et al. 2003). On the other hand, Brouillette et al. (2000) concluded that oximetry could be used to diagnose OSA for children with a positive predictive value of 97%, but a negative oximetry result cannot be use to rule out OSA.

In this study, we aimed to construct a predictive model for clinical prediction of high-risk OSA patients using fewer parameters (channels) by home-styled devices to diagnose some of severe patients followed by PSG examination to discriminate normal, mild, and moderate patients. Compared to the traditional setting that all suspected patients have to take PSG examination, the proposed scheme takes the advantage of simple and cheap home monitoring devices applied in

OSA diagnosis for reducing healthcare cost and increasing diagnostic efficiency. According to the cost-benefit and risk analyses, the proposed scheme has demonstrated to have a great potential in reducing healthcare cost, increasing efficiency, and eliminating insomnia effect caused by environmental change for some patients when tested in the sleeping center.

2. Materials and Methods

This study was designed to compare the benefits between the traditional PSG examination which only can be done in the sleeping center and a new proposed scheme that pulse oximetry is tested at home followed by the PSG examination. The logical thinking and study design process are shown in **Figure 1**. The study subjects, physiological signal measurements, and analytical techniques are described as follows.

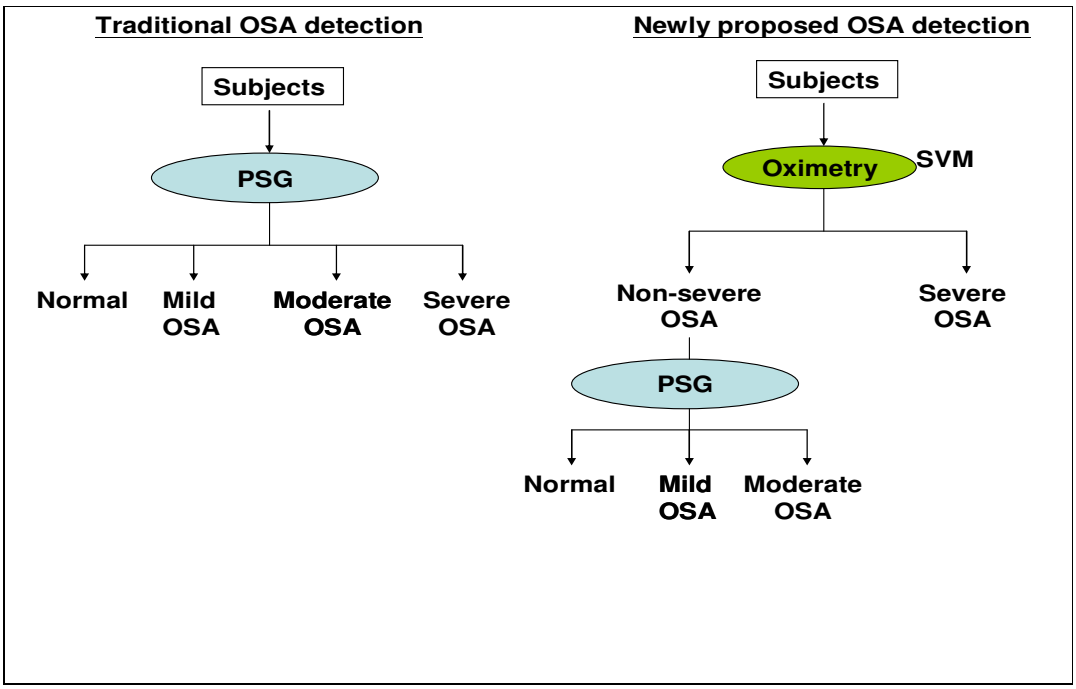

Figure 1. Proposed method for diagnosing patients with OSA.

Study Subjects

A total of 699 patients with possible OSA have been recruited and tested using PSG devises for overnight attending recording at the Sleep Center of one medical center in middle Taiwan from Jan. 2004 to Dec. 2005. Forty-eight subjects whose ages less than 20 or more than 85 years old were excluded from the study (Lam et al., 2006). Hence only data obtained from 651 patients

were used for further analysis. In order to compare the effect of not enough sleeping time, patients with sleeping time less than 4 hours were also excluded, resulting in a total of 561 patients for analysis. The study has been approved by Institute of Reviewing Board (IRB) of China Medical University.

Physiological Signal Measurements

Traditional measurements with PSG only: Alice 4 PSG recorder (Respironics Inc., USA) was used to monitor and record patient PSG, during which a number of physiologic variables are measured and recorded during sleep. Physiologic sensors are used to record (1) EEG for detecting brain electrical activity and sleep staging on the basis of 30-sec epochs, (2) EOG and submental EMG for detecting eye and jaw muscle movement, (3) tibia EMG for monitoring leg muscle movement, (4) airflow for detecting breath interruption, (5) inductance plethysmorgraphy for estimating respiratory effort (chest and abdominal excursion), (6) ECG for measuring heart rate, and (7) arterial oxygen saturation by using oximeter.

Proposed measurements with home oximetry followed by PSG: Demographic (age, gender, etc.), questionnaires of Epworth scaling score (ESS), and symptom questionnaires related to OSA diagnosis were filled by the patients before PSG recording. Anthropometric (weight, height, BMI, waist, neck and hip circumfences, etc.) were also measured and checked by the technicians. Here we aim to investigate the sensitivity of the proposed policy with an eximeter being brought home for over-night measurement to detect severe patients followed by PSG examination for diagnosing mild and moderate OSA patients. Since the cost of a PSG examination is much higher than oximetry test, it is expected to be cost-effective for the proposed policy.

Analytical techniques

Demographic and anthropometric data of patients were analyzed using descriptive statistical analysis for calculating means and standard deviations of individual variables. Inferential statistical analyses including *t*-test, univariate analysis, and multiple regression analysis were also

applied to detect significant variables for further discriminating among normal subjects and mild, moderate, and severe OSA patients and for diagnosing severe patients (AHI>=30) and combined moderate and severe patients (AHI>=15).. Finally, support vector machine was used to construct a predictive model based on the selected variables for developing a cheap computer-assisted diagnostic system.

Support vector machine

The Support vector machine (SVM) technique was first developed by Vapnik and his group in former AT&T Bell Laboratories. It is a useful technique for data classification and regression and has become an important tool for machine learning and data mining. In general, SVM has better performance when competed with existing methods, such as neural networks and decision trees (Brown et al., 2000; DeCoste & Schuolkopf, 2002; Lecun et al., 1995). Recently, application of SVM in medicine has grown rapidly. For examples, it has been applied in prediction of RNA-binding sites in proteins (Tong, Jiang, & Lu, 2008), discrimination of malignant and benign cervical lymph nodes (Zhang, Wang, Dong, & Wang, 2008), disease diagnosis using tongue images (Zhi, Zhang, Yan, Li, & Tang, 2007), and diagnoses of cardiovascular disease (Eom, Kim, & Zhang, 2008) and breast cancer (Polat & Gunes, 2007). The support vector machine (SVM) is a supervised learning method widely used for classification (Vapnik, 1995; Chang and Lin, 2001). A special property of SVM is that it can simultaneously minimize the empirical classification error and maximize the geometric margin. Its goal is to separate multiple clusters with a set of unique hyperplanes with greatest margin to the edge of each cluster, where each hyperplane separating two cluster is not unique for ordinary linear classifiers.

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Given a two-class linearly separable problem, the hyperplane separating two classes leaving the maximum margins from both classes is represented as (Theodoridis and Koutroumbas, 2003; Cristianini and Shawe-Taylor, 2000):

$$g(\mathbf{x}) = \mathbf{w}^T\mathbf{x} + w_0 = 0 \qquad (1)$$

The training data of two classes can be represented as ($\mathbf{x}_i$, y_i) with $\mathbf{x}_i \in \boldsymbol{R}^n$, $y_i \in \{+1,-1\}$, and i=1,2,…N, in which sample $\mathbf{x}_i$ is an N-dimensional input vector and y_i is its corresponding label indicating the class of $\mathbf{x}_i$. By scaling the orthogonal vector $\mathbf{w}$ and bias w_0 in Eq. (1) to make the values of g($\mathbf{x}$) at the nearest points in class 1 and class 2 equal to 1 and -1, respectively, the problem of obtaining the optimal hyperplane becomes a nonlinear quadratic optimization problem, which can be formulated as:

$$\underset{\mathbf{w},w_0}{\text{Min}} \ \frac{\|\mathbf{w}\|^2}{2}, \ \text{Subject to} \ \ y_i(\mathbf{w}^T\mathbf{x}_i + w_0) \geq 1, \ \ i = 1,2,...,N \qquad (2)$$

The problem can be solved by considering Lagrangian duality and be stated equivalently by its Wolfe dual representation form with the constraints satisfying the Karush-Kuhn-Tucker (KKT) conditions, i.e. $\partial L(\mathbf{w}, w_0, \boldsymbol{\lambda})/\partial \mathbf{w} = 0$, $\partial L(\mathbf{w}, w_0, \boldsymbol{\lambda})/\partial w_0 = 0$, $\lambda_i[y_i(\mathbf{w}^T\mathbf{x}_i + w_0) - 1] = 0$, and $\lambda_i \geq 0$ for $i = 1,...N$:

$$\text{Max } L(\mathbf{w}, w_0, \boldsymbol{\lambda}) = \frac{\|\mathbf{w}\|^2}{2} - \sum_{i=1}^{N} \lambda_i[y_i(\mathbf{w}^T\mathbf{x}_i + w_0) - 1] \qquad (3a)$$

$$\text{Subject to } \mathbf{w} = \sum_{i=1}^{N} \lambda_i y_i \mathbf{x}_i, \ \sum_{i=1}^{N} \lambda_i y_i = 0, \text{ and } \ \lambda_i \geq 0 \text{ for } i = 1,...N \qquad (3b)$$

where $L(\mathbf{w},w_0,\boldsymbol{\lambda})$ is a Lagrangian function and $\boldsymbol{\lambda}$ is the vector of Lagrangian multipliers corresponding to the constraint in Eq.(2). In contrast to Eq. (2), the first two constraints in Eq. (3) become equality constraints and make the problem easier to handle. Finally, by substituting the first two constraints in (3b) into (3a), the problem is formulated below:

$$\begin{aligned} &\underset{\boldsymbol{\lambda}}{\text{Max}}\left(\sum_{i=1}^{N}\lambda_i-\frac{1}{2}\sum_{i,j=1}^{N}\lambda_i\lambda_j y_i y_j \mathbf{x}_i^T\mathbf{x}_j\right), \\ &\text{Subject to } \sum_{i=1}^{N}\lambda_i y_i=0 \text{ with } \lambda_i\geq 0, i=1,...N \end{aligned} \tag{4}$$

As soon as the Lagrangian multipliers have been obtained by maximizing the above equation, the optimal hyperplane can be obtained from $\mathbf{w}=\sum_{i=1}^{N}\lambda_i y_i\mathbf{x}_i$ in Eq. (3). Once the optimal hyperplane has been obtained, classification of a sample is performed based on the sign of the following equation:

$$f(\mathbf{x})=\text{sgn}(\mathbf{w}^T\mathbf{x}+w_0)=\text{sgn}\left(\sum_{i=1}^{Ns}\lambda_i y_i\mathbf{x}_i^T\mathbf{x}_i+w_0\right) \tag{5}$$

where *Ns* is the number of support vectors.

For a nonlinear classification problem, the optimization problem shown in Eq. (2) is changed to:

$$\begin{aligned} &\underset{\mathbf{w},w_0}{\text{Min}}\left(\frac{\|\mathbf{w}\|^2}{2}+C\sum_{i=1}^{N}\xi_i\right), \\ &\text{Subject to } \; y_i(\mathbf{w}^T\phi(\mathbf{x}_i)+w_0)\geq 1-\xi_i, \text{ and } \xi_i\geq 0, \; i=1,2,...,N \end{aligned} \tag{6}$$

where C is a positive penalty parameter, variables ξ_i with $i= 1,\ldots,N$ are used to weight the cost of misclassified samples, and $\phi(\mathbf{x}_i)$ is a function applied to map the training sample $\mathbf{x}_i$ to a higher dimensional space. For a vector $\mathbf{x}\in R^n$ in the original feature space, it is assumed that there exists a function ϕ for mapping $\mathbf{x}\in R^n$ to $\mathbf{y}=\phi(\mathbf{x})\in R^k$ with $k > n$. Then, the following formula is true

$$\sum_r \phi_r(\mathbf{x})\phi_r(\mathbf{z})=K(\mathbf{x},\mathbf{z}) \tag{7}$$

where $\phi_r(\mathbf{x})$ is the rth component of the mapping and $K(\mathbf{x},\mathbf{z})$ is a symmetric function satisfying the following condition:

$$\int K(\mathbf{x},\mathbf{z})g(\mathbf{z})d\mathbf{x}d\mathbf{z}\geq 0, \;\; \text{and} \int g(\mathbf{x})^2 d\mathbf{x}\leq\infty \tag{8}$$

Finally, the optimization problem in Eq. (4) is reformulated as:

$$\begin{aligned} &\underset{\boldsymbol{\lambda}}{\text{Max}}\left(\sum_{i=1}^{N}\lambda_i-\frac{1}{2}\sum_{i,j=1}^{N}\lambda_i\lambda_j y_i y_j K(\mathbf{x}_i^T\mathbf{x}_j)\right), \\ &\text{Subject to } \sum_{i=1}^{N}\lambda_i y_i=0 \text{ with } 0\leq\lambda_i\leq C \end{aligned} \tag{9}$$

For a nonlinear classifier, various kernels including polynomial, radial basis function, and hyperbolic tangent can be used for mapping the original sample space into a new Euclidian space with Mercer's conditions are satisfied. The linear classifier can then be designed for classification. Among them, radial basis function, as shown in the following equation, is the most widely used function and is applied in this study for feature mapping.

$$K(\mathbf{x},\mathbf{z}) = \exp(-\gamma\|\mathbf{x}-\mathbf{z}\|^2) \quad (10)$$

Cross validation of the SVM model is achieved by dividing the data into *n* folds (clusters), in which *n*-1 folds are used for training the model while 1 fold for testing. For example, consider a data set which contains 600 samples and 6 folds are used for constructing and validating the model, in which each fold consists of 100 samples that 500 will be used for training and 100 for testing the prediction rate of the model.

3. Experimental Results

In the first experiment, the tested subjects were divided into 4 groups based on AHI values. Table 1 shows 6 variables, including age, body mass index (BMI), neck circumference, ESS, Oxyhemoglobin desaturation index (ODI), and heart rate, which reach significant level ($p<0.05$) after ANOVA test. The variables were then used as independent variables for SVM classification and for the prediction of normal (AHI<5) and different degrees of OSA severity including mild (5 ≦AHI<15), moderate (15≦AHI<30), and severe (30≦AHI).

Table 1. ANOVA tests of demographic, questionnaire, and PSG data obtained from patients across four stages of severity based on AHI value

	AHI <5 (n= 75)		**5≦AHI<15 (n= 134)**		**15≦AHI<30 (n= 133)**		**AHI ≧30 (n= 309)**		**Test (ANOVA)**
Gender									
Female	33 (44%)		52 (38.81%)		31 (23.31%)		31 (10.03%)		$X^2 = 64.734$, $p<0.001$
Male	42(56%)		82(61.19%)		102 (76.69%)		278(89.97%)		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age	36.12	10.35	42.36	11.44	45.88	12.79	48.13	12.32	(1)<(2),(3),(4) (2)<(4)
BMI	23.99	3.16	25.61	3.74	26.16	3.70	28.56	8.81	(1),(2),(3)<(4)
Neck Circum.	36.29	3.44	37.61	3.63	38.70	3.19	40.74	3.08	(1)<(3),(4) (2)<(4), (3)<(4)
ESS	7.76	5.13	8.54	4.70	9.15	5.27	10.01	5.33	(1)<(4)
ODI	1.21	1.50	5.22	3.88	12.01	7.62	45.65	25.34	(1)<(2)<(3)<(4)
Heart Rate	70.67	8.61	71.15	10.63	72.60	9.52	75.23	11.75	(1),(2)<(4)

Regarding the influence of gender in severity of OSA, as depicted in Table 1, the number of male is more than the female for the abnormal compared to the normal, especially for more severe stages. In addition, variables including age, BMI, neck circumference, ESS, heart rate, and

ODI reach levels of significant differences ($p<0.05$) among two or three stages. However, only ODI can be used to differentiate all of the 4 stages.

3-1 Discrimination of normal subjects and mild, moderate, and severe patients

The confusion matrices of 4 OSA stages using ODI are shown in Table 2 for two datasets with 651 and 561 samples, respectively. It was observed that although various combinations of neck circumference, BMI, ESS, and ODI have been used for constructing predictive models, applying ODI alone as the predictor achieves similar prediction rate. This indicates that demographic information and questionnaires are not very useful in elevating the predicting efficiency. It was found that the predictive rate of diagnosing severe patients is high for both datasets consisting of 651 (accuracy: 88.25%) and 561 (accuracy: 86.46%) samples, respectively. The cross validation procedure was repeated for 10 times.

Table 2. Confusion matrices for classification of 4 groups with ODI used as predictor for two datasets with 651 and 561 samples, respectively. The matrix was obtained with 2-fold cross validation and repeated for 10 times. The predictive rates for normal and mild are better for the dataset with 561 samples, while the prediction rate of severe patients is better for the dataset with 651 samples.

Table 2. Confusion matrices for classification of 4 groups with ODI used as predictor for two datasets with 651 and 561 samples, respectively

N=651	N_{avg}	Normal	Mild	Moderate	Severe	Accuracy (%)
Normal	37	24.2	12.6	0.2	0	65.41
Mild	67	13.3	39.6	13.3	0.8	59.10
Moderate	66	2.5	21.1	27.6	14.8	41.82
Severe	154	0.9	5.5	11.7	135.9	**88.25**
Total Validation	324					70.15
N=561	N_{avg}	Normal	Mild	Moderate	Severe	Accuracy (%)
Normal	35	25.8	9.1	0.1	0	**73.71**
Mild	63	10.2	42.3	10.1	0.4	**67.14**
Moderate	57	1.5	18.6	23.9	13.0	41.93
Severe	127	0	5.9	11.3	109.8	86.46
Total Validation	282					**71.56**

3-2 Diagnosis of severe patients

The subjects were divided into two groups using AHI=30 as the threshold to discriminate severity of OSA that the subjects were classified into non-severe (AHI<30) and severe (AHI>=30) groups. As shown in Tables 3, the successful prediction rates achieve 89-90% for different combination of independent variables. Again, it was found that ODI alone provides similar predictive accuracy (89-90%) and sensitivity (94-95%) for the diagnosis of severe OSA patients.

Table 3. Diagnosis of severe patients using different combination of salient features

Data	Predictive Index (%)	NC, BMI, ESS, ODI	ODI, ESS	ODI, BMI	ODI
Dataset 1 (N=651)	Accuracy	90.19	90.06	89.41	89.94
	Sensitivity	94.24	94.06	94.24	**95.06**
	Specificity	85.71	85.65	84.09	84.29
Dataset 2 (N=561)	Accuracy	89.40	89.11	89.43	89.04
	Sensitivity	94.13	93.68	95.16	94.52
	Specificity	83.62	83.54	82.44	82.36

3-3 Diagnosis of severe and moderate patients

In this experiment, the subjects were divided into two groups with AHI=15 used as the threshold to discriminate severity of OSA by classifying the subjects into normal and mild (AHI<15) and moderate and severe (AHI>=15) groups. As shown in Tables 4, the successful prediction rates achieve about 86-87% for different combination of independent variables. Again, ODI alone provides similar predictive performance to other combinations of variables.

Table 4. Diagnosis of severe and moderate patients using different combination of salient features

Data	Predictive Index (%)	NC, BMI, ESS, ODI	ODI, ESS,	ODI, BMI	ODI
Dataset 1 (N=651)	Accuracy	86.45	86.51	86.60	86.64
	Sensitivity	85.96	85.38	87.02	87.12
	Specificity	86.68	87.05	86.41	86.41
Dataset 2 (N=561)	Accuracy	86.17	86.70	87.27	87.05
	Sensitivity	85.61	87.45	88.27	88.57
	Specificity	86.46	86.30	86.74	86.25

4. Discussions

As shown in the previous section, ODI alone provides good prediction in the diagnosis of OSA, while demographic and questionnaire variables are not very helpful to elevate the prediction rate, as reported by Lin et al. (2009). In addition, prediction accuracy using SVM is much higher than traditional linear discriminant.

4.1 Cost Benefit Analysis

As shown in Table 2, with regard to detection of normal, mild, moderate, and severe patients, the mean prediction rate achieves more than 86% in the detection of severe OSA patients, while there are only 40%-74% accuracy in detecting other three groups of subjects. Furthermore, as indicated in Table 3, for a two-class SVM classifier, the sensitivity in diagnosing severe OSA patients achieves as high as 94-95%. It is promising for oximetry to be used as a predictor for the diagnosis of severe patients, but not sensitive enough to detect normal patients. Taking the dataset containing 651 samples as an example, as shown in Table 3, among them, 95.06% (293) of the severe patients (309) who need to be treated immediately are expected to be diagnosed based on the oximetry. Regarding the whole population of this investigation, the percentage of severe patients is 309/651=47.47%, among them 95.06% can be detected; that is 47.47% x 95.06% = 45.12% of the total population who are suspected to have OSA can be accurately diagnosed as severe patients.

The sensitivity in detecting severe patients is 95.06%, which indicates that 4.96% of the subject will be treated as normal, mild, or moderate even they are severe. Further PSG test will be expected to diagnose these patients. On the other hand, the percentage of normal, mild and moderate patients who are diagnosed as severe is 15.71% (1–specificity) which accounts to 342/651 x 15.71%= 8.25% of the total population. According to Table 2, none of the normal subjects were diagnosed as severe patients, which indicated that the subjects being diagnosed as severe were mild or moderate OSA patients. Therefore, it is acceptable for this miss diagnosis since some investigations suggest that mild and moderate patients also need treatment using CPAP. We suggest that oximeter is efficient to be used for diagnosing severe OSA patients.

In conclusion, the predictive model is suitable for predicting severe patients using cheaper oximetry while the non-severe patients including normal, mild, and moderate patients are needed to be confirmed using more expensive PSG. Based on the current health insurance payments in Taiwan, the expense for taking a PSG examination is NT$4560 while it takes only NT$480 for oximeter. Hence the average cost per case for OSA detection is 480 x (45.12%) + (480 + 4560) x (1 -45.12%) = NT$2983. The cost is lower than the situation that all the subjects are examined using PSG with a saving of NT$1577 (34.58%) for each case.

4.2 Consideration of Sleeping Time

Subjects who do not have enough sleep time during the experiment might have influence on accurate prediction of OSA severity. In this experiment, among the 651 subjects, 85 who have sleeping time less than 4 hours may be excluded (Lam et al. 2006). Table 5 compares the number and percentage of subjects with sleeping time less than and more than 4 hours threshold.

Table 5. A comparison of distribution of subjects based on length of sleeping time

Sleeping time		**Normal**	**Mild**	**Moderate**	**Severe**
<4 hr	Number	5	7	18	55
(n=85)	Percentage	5.88%	8.24%	21.18%	64.7%
≧4 hr	Number	70	127	115	254
(n=566)	Percentage	12.37%	22.44%	20.32%	44.88%
Polled	Number	75	134	133	309
(n=651)	Percentage	11.52%	20.58%	20.40%	47.47%

Although Lam et al. (2006) excluded subjects with sleeping time less than 4 hours, the reason why these data were removed is not reported. Here, we compare two groups, one is consisted of the subjects who slept less than 4 hours (SL) and the other contains subjects who have slept more than 4 hours (SM). By analyzing the data shown in Table 8 using contingency table X^2 statistical test, the result shows that significant difference (p<0.001) exists between two groups (chi-square = 16.1 and degrees of freedom = 3). As indicated in the table, the percentage of severe patients in the SL group (64.70%) is higher than the SM group (44.88%), while it has opposite effect by considering the cumulated normal and mild subjects (14.12% for SL v.s. 34.81% for SM). On the other hand, the percentages of moderate patients are very close between two groups (21.18% v.s. 20.32%).

As depicted in Table 6, unpaired t-test was used to further compare salient variables of two groups. Among them, no significant difference (p>0.05) was found for anthropometric data, i.e. BMI and NC, ESS, and HR, while significant difference was found for age, ODI, and AHI. It indicates that aged subjects are liable to have insomnia and have more severe OSA with higher ODI and AHI.

Table 6. Statistic analysis using unpaired *t*-test to test salient variables

Sleeping Time		**Age**	**BMI**	**NC**	**ESS**	**HR**	**ODI**	**AHI**
<4 hr	Mean	52.02	27.19	39.72	9.55	33.00	74.23	44.95
(n=90)	STD	14.45	4.26	3.82	5.45	26.09	12.31	27.55
≧4 hr	Mean	44.06	26.90	39.07	9.23	24.19	73.23	33.13
(n=561)	STD	12.00	7.11	3.62	5.19	26.40	10.69	28.19
***p* value**		**.0001**	.7144	.1269	.5987	.4311	**.0042**	**.0003**

There are two possible explanations of this finding: (1) some severe patients tend to sleep less because of early apnea or hypopnea occurrence and (2) data recorded from subjects who do not have enough sleeping time are not reliable for further analysis. Regarding the first possibility, the early occurrence of apnea or hypopnea after having fallen asleep induces insomnia for severe patients. The environmental change might also be the reason for causing insomnia. By observing the latency time in Table 7, significant difference (p<0.0001) can be found between two groups. Subjects with less sleeping time demonstrate greater latency. Although arousal counts for SL group is significantly smaller than the SH group (p<0.0001), the arousal index (arousal counts per hour), however, is significantly greater (p<0.0042). We suggest that subjects who were diagnosed as normal but didn't take enough sleeping time in the sleeping center might be caused by environmental change and should have another PSG test. By using oximeter to test OSA at home might be able to eliminate such variation.

Table 7. Statistic analysis using unpaired *t*-test for testing arousal and sleeping latency

Sleeping Time		**Latency**	**Arousal Count**	**Arousal Index**
<4 hr	Mean	39.88	107.06	40.13
(n=90)	STD	38.80	75.44	22.31
≧4 hr	Mean	16.52	163.11	33.19
(n=561)	STD	14.41	102.26	20.53
***p* value**		**.0001**	**.0001**	**.0042**

With regard to the second possibility, the data collected from the 90 subjects who had sleeping time less than 4 hours were removed and resulted in a total of 561 subjects for further analysis. The percentage of patients without enough sleeping time accounts to 13.82%. To compare the accuracy in detecting 4 different groups in Table 2, great changes can be observed with regard to normal (65.41% vs 73.71%) and mild (59.10% vs 67.14%) groups, while only small variation for moderate (41.82% vs 41.93%) and severe (88.25% vs 86.46%) groups. However, as indicated in Tables 3 and 4, no significant influence is found for detecting severe groups and combined moderate and severe group. The effect of patients whose sleeping time less than 4 hours needs to be further investigated.

Unlike PSG and single-lead ECG (Thomas et al. 2005), the limitation of oximetry measurement is that it cannot score sleep quality. Standard PSG scores sleep quality based on EEG signal analysis by grading the sleep quality into 4 stages of continuum of depth during non-REM sleep. Thomas et al. (2005) suggested that sleep could be identified as wake/REM, cyclic alternating pattern (CAP), and non-CAP based on the Fourier analysis of R-R interval series and its associated ECG-derived respiration (EDR) signal. However, the main advantage of using oximetry as predictive parameter is its great sensitivity in detecting severe OSA patients

with cheaper price compared to PSG.

4.3 Study Limitation

Among the 651 subjects studied, only 75 were verified as normal which accounts for only 11.52% of the total subjects. This is quite normal since the subjects suspected to have OSA were recruited from the outpatients. Another limitation is that all events found in PSG were verified by technicians work in the sleep center. The variation occurred among different technicians cannot be avoided and negleted since each one has his/her subjective judgment. Therefore, design of an objective computer-assisted system is needed for eliminating the loads and subjective opinions of individual technicians.

As discussed in Section 4.2, analyzed results for subjects whose sleeping time less than 4 hours are significantly different form the results obtained from subjects with more sleeping time. In this study, the data collected for subjects with less sleeping time are included, which might affect the results of this study. However, some data obtained from subjects without enough sleeping time seem to have diagnostic value, especially for those with severe OSA. Further investigation on normal or less severe patients is needed for determining if these subjects should take more tests.

5. Conclusion and Future Works

In addition to ODI, other variable such as heart rate variability (HRV) for quantizing sympathetic tone was also suggested as a useful parameter in the evaluation of OSA. Future work will test this parameter to verify if it is a valuable parameter. It will be accompanied with ODI for constructing a predictive model for OSA diagnosis if it has been verified as an effective parameter.

In previous section, we have demonstrated that the variables, such as age, ODI, and AHI, obtained from subjects without enough sleeping time is significantly different from those whose sleeping time is more than 4 hours. The former group tends to be more severe than the latter group. More PSG tests are needed to confirm if the test with sleeping less than 4 hours is valid for OSA diagnosis.

Based on the cost-benefit analysis, we suggest that home-styled oximetry alone can be used for sifting severe patients which will be followed by PSG to discriminate normal, mild, and moderate subjects with a total cost down of 35.72%. More large scale experiment and rigorous analysis are needed to see the proportion of normal subjects will be incorrectly diagnosed as severe.

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