中國醫藥大學

醫務管理學研究所碩士論文

依序利用Oximetry及PSG診斷阻塞性睡眠缺氧症以降低醫療成本

Diagnosis of Patients with Obstructive Sleep Apnea Using Pulse Oximetry Followed by Polysomnography for Cost Reduction

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中文摘要

阻塞性睡眠呼吸中止症（OSA）是造成車禍的重要原因，患者之肇事率比正常人提高約 2-7 倍，它同時也是罹患許多慢性病的重要原因。睡眠多項生理檢查（PSG）是一項診斷檢查，它可以測量及記載睡眠時的多個生理變項，它被視為診斷阻塞性睡眠呼吸中止症（OSA）的最佳標準，但其缺點為非常費時且價格昂貴。本研究之主要目的為利用問卷和簡單便宜的家庭式診斷工具來預測高危險群的 OSA 患者，除了對於降低醫療費用有很大的潛力之外，也可以避免某些病人因睡眠環境的改變所造成之影響。

本實驗對於 2004 年 1 月至 2005 年 12 月期間 699 個疑似 OSA 的病人，利用 PSG 在醫院睡眠中心進行測試。其中，對於 48 個年齡在 20 歲以下或 85 歲以上之病人資料予以排除，因此僅剩下 651 個病人資料進行後續分析。進行統計分析及特徵篩選之後，利用支援向量機 (SVM)進行分類以區分正常及不同嚴重程度之病患。

研究的初步結果顯示，血氧不飽和指數(Oxyhemoglobin Desaturation Index, ODI)是最好的預測參數。對於嚴重的 OSA 病患而言，其靈敏度（Sensitivity）高達 87.20％，但用於區別正常與不正常的病人，其靈敏度卻只有 70.39％，其他的人口學特性、身體特徵之量測變項及問卷對預測率並沒有提升的效用。經成本效益分析後發現，我們建議可以第一階段以家庭式的血氧濃度偵測器有效診斷重度 OSA 的病患，然後再利用 PSG 偵測正常、輕度及中度之病患。利用本論文所建議的方式，以目前台灣的健保收費規範下，可以降低診斷成本達 35.72%。

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 time-consuming and expensive. Therefore, clinical prediction of high-risk OSA patients using questionnaires and cheap home diagnostic devices has a great potential in reducing healthcare cost and in eliminating environmental variation for some patients tested in the sleeping center.

In this study, 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. Therefore only the data of 651 patients were used for further analysis. After statistical analysis and feature selection, support vector machine (SVM) was then used to discriminate normal subjects and patients with different stages of severity.

The results show that oxyhemoglobin desaturation index (ODI) alone has the best prediction outcome for the patients with severe OSA with a sensitivity as high as 87.20%. The sensitivity is only 70.39% in discriminating the normal from abnormal subjects. Based on the cost-benefit analysis, we suggest that home-styled oximeter can be used for sifting severe patients from all suspected patients at the first stage, which is then followed by PSG for discriminate normal subjects and mild

and moderate patients. It was found that a cost reduction of NT$1629 (35.72%) per case in average can be achieved under the current Taiwanese insurance setting.

Keywords：

Obstructive sleep apnea ； Oximetry ； Support Vector Machine(SVM)；Polysomnography (PSG)

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Chapter 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). OSA is a significant cause of motor vehicle crashes resulting in increased risk of 2-7 folds (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).

The severity of the respiratory events is measured by the frequency and duration of apneas and hypopneas per hour of sleep, namely apneas and hypopneas index (AHI), using PSG. Apnea was defined as a cessation of air flow for at least 10 seconds while hypopnea as a decrease of abdominal movement for more than 10 seconds associated with either a reduction in Oxyhemoglobin saturation for more than 4% or an arousal

(Netzer et al. 2001). The airway is only partial obstructed resulting in airflow limitation for hypopnea. The event with up to 600 apneas per night has been found for patient with severe OSA (Huupponen et al. 2006). Another generally used index is the respiratory disturbance index (RDI), which, in addition to apnea and hypopnea, quantifies less evident respiratory events, for example, respiratory effort-related arousal characterized by increasing respiratory effort for 10 or more seconds leading to an arousal not meeting to apnea and hypopnea criteria (Fleisher and Krieger, 2007).

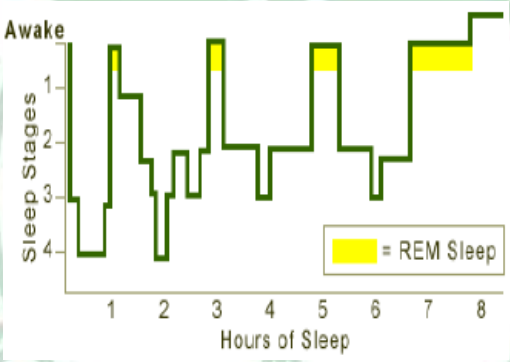
Subjects with AHI smaller than 5 are considered as normal while AHI greater than 5 and smaller than 15 as mild. The patients with AHI between 15 and 30 and greater than 30 are diagnosed as moderate and severe, respectively (American Academy of Sleep Medicine Task Force, 1999).

1.1. Sleep Medicine

Sleep is defined as a state of consciousness in which the brain is relatively more responsive to internal than to external stimuli. It is divided into REM and non-REM sleeps. As illustrated in Fig. 1, non-REM sleep is further divided into 4 sleep stages, including Stage I (theta wave), Stage II (sleep spindle and K complex), Stage III (delta wave), and Stage IV (delta wave), and is followed by rapid eye movement (REM) sleep. Although the ratio of NREM to REM varies from cycle to cycle, the sequence makes up one sleep cycle lasting for about 90 minutes (Russo, 2005).

The fully restorative sleep time for adult is 8-8.4 hours, while in infant the total sleep time is greater than other age groups. For newborn babies, the total sleep time is between 14 to 16 hours a day. For adult, REM represents 20-25% of total sleep time. Stage I sleep occurs at the

beginning of the sleep and during brief arousal periods within sleep, which usually includes 5-10% of the total sleep time. Stage II accounts for 40-50% of total sleep time and occurs throughout the sleep period. In contrast, Stages III and IV sleep mostly occur in the first third of the night and represent up to 20% of total sleep time. The difference between Stages III and IV is the percentage of delta activity. Compared to young adults, the overall sleep time is decreased with the time spent in stages III and IV sleep decreases by 10–15% for elderly persons, while the time in stage II increases by 5%. Additionally, the latency to fall asleep and the frequency and duration of arousal increase resulting in an increase of duration of fully restorative sleep (Russo, 2005).



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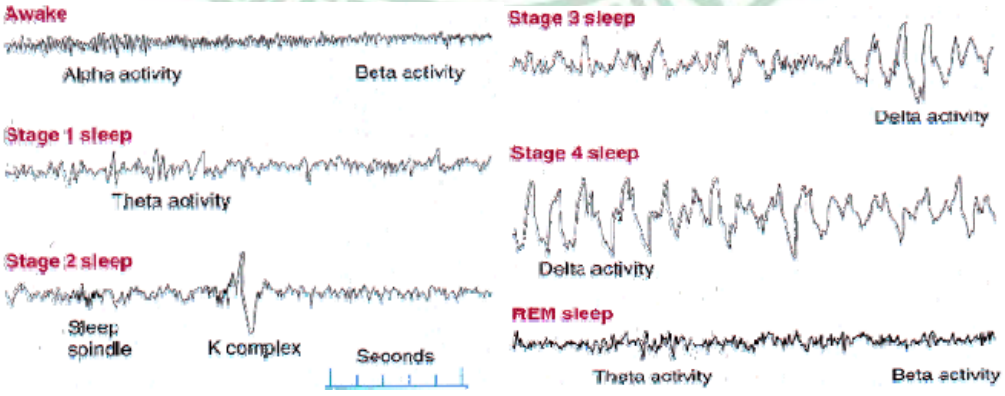


(b)

Figure 1 (a) Sleep is divided into REM and non-REM sleeps; (b) EEG of awake, REM, and various stages of non-REM sleep.

1.2. Polysomnographic Recorders

Polysomnography (PSG) (Type I) 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 mentioned above 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 sifting OSA. In Table 1, 3 types of portable monitoring devices are compared.

Table 1 Portable monitoring devices (Chesson et al., 2003)

Type of Device	**Name**	**Parameters Measured**
Type 2	Comprehensive Portable	Minimum of 7 channels, including EEG, EOG, chin EMG, ECG for heart rate, airflow, inductance plethysmorgraphy for recording respiratory effort, and arterial oxygen saturation
Type 3	Modified Portable Sleep Apnea Testing	Minimum of 4 channels, including ventilation or airflow (2 channels), heart rate or ECG, and oxygen saturation
Type 4	Continuous Single or Dual Bioparameters	One or two channels, typically including oxygen saturation and/or airflow

1.3. Prediction and diagnosis of OSA

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.

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).

1.4. Home diagnosis using Oximetry

As mentioned above, PSG is labor-intensive and time-consuming. Additionally, it has several limitations, such as technical expertise is required and timely access is restricted (Flemons et al., 2003). Thus, several alternative and simpler diagnostic devices have been evaluated. Home pulse oximetrer has been proposed as a valuable screening tool despite 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). 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). 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.

Although a Type 4 portable monitoring device which embeds only one or two channels were not recommended in either attended or unattended settings (Chesson et al., 2003), a study indicated that PSG is not better than oximetry in the diagnosis of OSA with the correct prediction rates for PSG and oximetry are 0.61 and 0.64, respectively (Whitelaw et al., 2005). In a more recent study, diagnosis and initial treatment of moderate to severe OSA patients were compared between PSG and ambulatory titration by combining auto-CPAP and oximetry (Mulgrew et al., 2007). It was shown that PSG and the ambulatory approach have no differences regarding the primary outcome, AHI, and secondary outcome evaluated after 3 months of treatment (Mulgrew et al., 2007).

Oxyhemoglobin desaturation index (ODI) was defined as oxygen desaturations per hour of sleep. Oximetry combined with other channel recordings such as microphone, airflow thermistor, and ECG; and questionnaires including ESS (Chervin and Aldrich, 1999), have been widely investigated. These findings showed that both schemes are unable to improve sensitivity and specificity of OSA diagnosis than using oximetry only (Series et al., 1999; Baltzan et al., 2000). However, a previous report showed that combination of a questionnaire and pulse oximetry increases the specificity of oximetry as a screening tool for sleep apnea (Nuber et al., 2000), hence controversy still exists (Netzer et al., 2001).

1.5. Pathology and Treatment of OSA

1-5-1 Pathology of OSA

OSA etiology in adults elicits increased upper airway resistance and airway closure caused by anatomic factors (Schellenberg et al., 2000; Kao et al., 2003; Schwab et al., 2003) and physiological factors that induce dysfunction of airway-dilating muscles and collapsibility of airway (Lindman and Stal, 2002; Mortimore and Douglas, 1997). The former includes pathological factors occurred in nose, tongue, lateral pharyngeal walls, soft palate, tonsils, and parapharyngeal fat pads, whereas the latter is mainly caused by reduced reflex responses of tongue and soft palate muscles to negative airway pressure (Fleisher and Krieger, 2007).

OSA is highly associated with insulin resistance and metabolic syndrome for adults. It was found that visceral fat accumulation, a marker of insulin resistance, rather than subcutaneous adiposity is strongly associated with OSA (Shinohara et al., 1997). In addition, adults who snore are more likely to develop type II diabetes mellitus and cardiovascular diseases (Al-Delaimy et al., 2002). It was also found that insulin resistance in obese children is associated with OSA and short sleep duration (Flint et al., 2007; De La Eva et al., 2002). However, compared to adults, pediatric OSA is usually caused by adenotonsillar hypertrophy (Guilleminault et al., 2005; Brouillette et al., 2000).

OSA is a risk factor for cardiovascular morbidities (Luthje and Andreas, 2007; Shahar et al., 2001; Peppard et al., 2000) including hypertension, pulmonary hypertension (Schultz et al., 2005; Atwood et al., 2004), atrial fibrillation (Gami et al., 2004), left ventricular diastolic dysfunction (Arias et al., 2005), myocardial infarction, heart failure (Bradley and Floras 2003), stroke (Yaggi et al., 2005), and sudden death (Gami et al., 2005). Autonomous imbalance such as elevated sympathetic activation for OSA patients is manifested with higher heart rates, less heart rate variability, and higher blood pressure than normal control subjects (Caples et al., 2005). Sympathetic activation was also identified

to have connection with impaired glucose tolerance and leptin resistance, which might explain that patients with OSA have higher fasting blood glucose level and greater risk in developing diabetes mellitus (Luthje and Andreas, 2007). Endothelial dysfunction is a precursor of arterial hypertension and has been reported to increase cardiovascular diseases (see Luthje and Andreas 2007 for review). Impairment of endothelial function has been observed in OSA patients with abnormally increased levels of endothelin-1 (Gjorup et al., 2007; Grebe et al., 2006; Nieto et al.. 2004; Phillips et al., 1999) which in turn induce hypertension and related cardiovascular disease.

Local disruption in the regulation of sleep in frontal lobes caused by apnea inducing hypoxia and hypercapnias was proposed (Huupponen et al., 2006). The pathology finding is manifested by inter-hemispheric spindle frequency difference in apnea patients. Spindles can be detected and observed by EEG with a mean duration of 1 second which originate from thalamus and then propagate to the cerebral cortex. Spindles are considered to be the events for maintaining sleep by blocking the transfer of sensory signals to the cerebral cortex during sleep (Jankel and Niedermeyer, 1985; Steriade, 1992).

1-5-2 Treatment of OSA

Continuous positive airway pressure (CPAP) is deemed as the most effective technique and is generally used as a tool for treating patients with OSA (Basner, 2007). In addition to having the effect in enlarging the airway by changing the dimension of the lateral pharyngeal walls (Schwab et al., 1996), it also increases the tone of the upper airway dilator muscles by reducing susceptibility to collapse (Mortimore and Douglas, 1997). Standard CPAP has constant inspiratory and expiratory pressures, while automated CPAP (APAP) is able to continuously adjust

pressure in providing better efficiency and compliance compared to CPAP titration (Masa et al., 2004). El Solh et al. (2007) used a general regression neural network (GRNN) to develop a predictive model for determination of optimal CPAP titration pressure, P_{prep}(ANN), which contrasts to traditional regression equation that the optimal CPAP pressure was calculated from the following equation:

$$P_{prep}(RE)=(0.16xNC)+(0.13xBMI)+(0.04xAHI)-5.12$$

In order to obtain real optimal pressure for comparison with P_{prep}(ANN) and P_{prep}(RE), the initial pressure of CPAP was set at a pressure of 4 cm H_2O and was gradually increased by 1 cm H_2O for every 20 minutes until the level that apnea, hypopnea, snoring, and recurrent oxyhemoglobin desaturation rather than arousal are eliminated. The optimal pressure, P_{opt}, was defined as the lowest pressure when the patient has an AHI<5 (El Solh et al., 2007). The results indicated that the correlation between P_{opt} and P_{prep}(ANN) was higher than the correlation between P_{opt} and P_{prep}(RE) (El Solh et al., 2007).

Treatment of OSA patients with CPAP was reported to have significant improvement on abnormal structural and functional consequence of heart characterized by increase in interventricular septum thickness, decrease in left ventricular stroke volume, and decrease of right ventricular tissue Doppler systolic velocity (Shivalkar et al., 2006). Central sleep apnea (CSA) is a less common sleep disorder that cyclic loss of central ventilatory driving force is lost. Pusalavidyasagar et al. (2007) discovered that although patients in both OSA and CSA groups have similar diagnostic AHI, AHI and central apnea during CPAP trial are significantly higher for patients with CSA than OSA (p<0.0001). Additionally, patients with CSA have more CPAP interface problems including CPAP mask removal and air hunger or dyspnea. These findings indicate that CSA patients may need better alternative treatment to

eliminate the central apnea events (Pusalavidyasagar et al., 2007).

If patients who are not adaptable to CPAP for medical or psychological reasons, removable oral appliance fitted to the teeth during sleep is also recommended as an efficient way to improve breathing disturbance, hypertension, and quality of life (Bloch, 2006). Additionally, reduction of excess weight for obese patient, upper airway surgery, and treatment of nasal obstruction for patients due to chronic rhinitis, nasal polyposis, or nasal sepal deviation are also alternative choices (Bloch, 2006). Although various soft tissue surgery used for treatment of OSA have been proposed, which, however, remains controversial. However, adeno-tonsillectomy has been successful performed in patients with adeno-tonsillar hypertrophy for both adult (Bloch, 2006) and children (Guilleminault et al., 2005; Taman et al., 2006).

Treatment of moderate OSA patients using acupuncture was also investigated by Freire et al (2007). Their finding indicates that acupuncture is effectively in the improvement of AHI and treatment of OSA. Results obtained from PSG and questionnaires (SF-36 and ESS) both demonstrate the above findings.

Medication administration was also used to treat patients with mild to moderate OSA, although it is insufficient to improve patients with severe OSA compared to CPAP (Sangal et al., 2007). Biogenic amine reuptake inhibitors, including protriptyline (non-selective norepinephrine reuptake inhibitor) and fluoxetine (selective serotonin reuptake inhibitor), were reported to be able to improve sleepiness for patients with OSA. One investigation reported that it barely improve RDI (Hanzel et al., 1991) while others had no objective changes (Brownell et al., 1982; Smith et al., 1983). Recently, Sangal et al. (2007) administrated atomoxetine, a selective norepinephrine reuptake inhibitor, to 15 subjects who have been diagnosed with sleep disorders and finished the complete study. Similar

to previous investigations, the results showed that atomoxetine significantly decrease sleepiness, quantified by ESS and clinical global impression (CGI), but did not significantly decrease RDI.

Pediatric OSA is usually caused by adenotonsillar hypertrophy (Guilleminault et al., 2005; Brouillette et al., 2000), hence adenotonsillectomy is often considered as alternative treatment in addition to CPAP (Guilleminault et al., 2005).

1.6. Motivations and Objectives

Oxyhemoglobin desaturation index (ODI) obtained from oximetry was defined as oxygen desaturations per hour of sleep. Oximetry combined with other channel recordings such as microphone, airflow thermistor, and ECG; and questionnaires including ESS (Chervin and Aldrich, 1999), have been widely investigated. These findings showed that both schemes are unable to improve sensitivity and specificity of OSA diagnosis than using oximetry only (Baltzan et al., 2000). However, a previous report showed that combination of a questionnaire and pulse oximetry increases the specificity of oximetry as a screening tool for sleep apnea (Nuber et al., 2000). Hence, controversy still exists.

Another motivation of this study is that a previous investigation found that the patients with severe OSA have the most benefit from CPAP (Patel et al., 2003) while patients with mild or unclear OSA have less treatment effect although AHI has been reported to be improved (Barnes et al., 2002; Monasterio et al., 2001). Orth et al. (2006) also reported that compliance is lower for patients with milder OSA. Hence, using simple oximetry to diagnose patients with severe OSA has potential benefit in reducing cost and attaining beneficial treatment effects for the severe patients.

The objective of this thesis is to construct a predictive model for clinical prediction of high-risk OSA patients using fewer significant

parameters (channels) accompanied with questionnaires so that simple home monitoring devices can be applied for OSA diagnosis. It is expected to have a great potential in reducing healthcare cost and eliminating environmental variation when tested in sleeping center for some patients.

1.7. Organization of Thesis

The rest of this thesis is organized as follows. In Chapter 2, subjects recruited, conceptual framework, and PSG recording method are described. The statistical analysis and support vector machine will be also addressed. The experimental results are presented in Chapter 3. Prediction of severe and non-severe patients using support vector machine (SVM) is demonstrated. Chapter 4 offers discussions regarding cost benefit analysis duration of sleeping time, and study limitation. Perspectives for future work are given in Chapter 5.

Chapter 2 Materials and Methods

2.1. 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 China Medical University Hospital 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. The study has been approved by Institute of Reviewing Board (IRB) of China Medical University.

2.2. Conceptual Framework

Figure 2 shows the conceptual framework of this investigation. Retrospective study was done by analyzing the data obtained within the period from Jan. 2004 to Dec. 2005. In this study, SPSS 12.0 software package was used to perform statistic analysis of the acquired data. Descriptive statistics was used to overview the characteristics of the data with mean and standard deviation calculated for each continuous variable. Frequency and percentage of each categorical variable were also calculated for further analysis. Inference statistics, such as Pearson chi-square test was used to test significance of categorical variables while ANOVA applied for detecting continuous variables with significance (p<0.05). Significant variables were selected for later construction of predictive model using support vector machine (SVM).

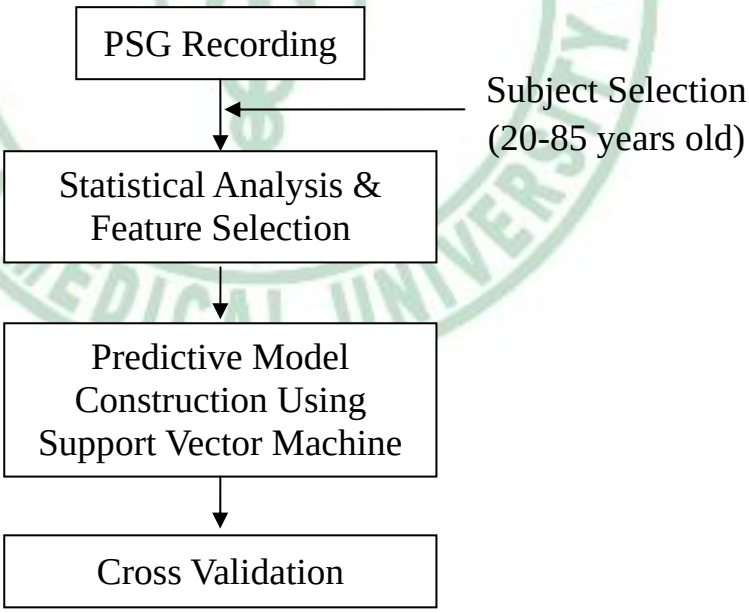


Figure 2 Conceptual framework

2.3. PSG Recording

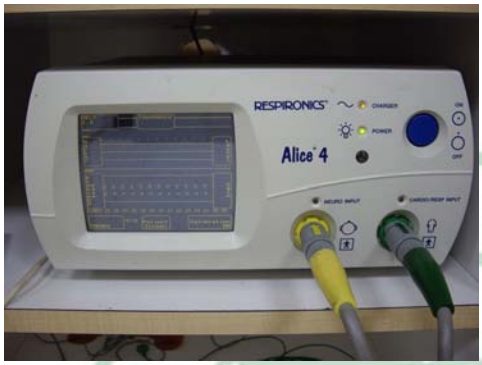
In this study, Alice 4 PSG recorder (Respironics Inc., USA) was used

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. Figure 3 (a) and (b) shows the PSG system and its junction box. In Fig. 3 (c), an example showing how electrodes of various channels are placed before clinical PSG recording is demonstrated. Figure 4 shows an example of various channels of acquired PSG signals.

2.4. Statistic Analysis and Feature Selection

As shown in Fig. 5, demographic (age, gender, etc.), questionnaires of Epworth scaling score (ESS), and symptom questionnaires related to OSA diagnosis which were filled by the patients before PSG recording. Anthropometric (weight, height, BMI, waist, neck and hip circumfences, etc.) were measured and checked by the technicians.

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 prediction and discrimination between normal and abnormal and between severe and non-severe patients. Finally, support vector machine was used to construct a predictive model based on the selected variables for developing a cheap computer-assisted diagnostic system.



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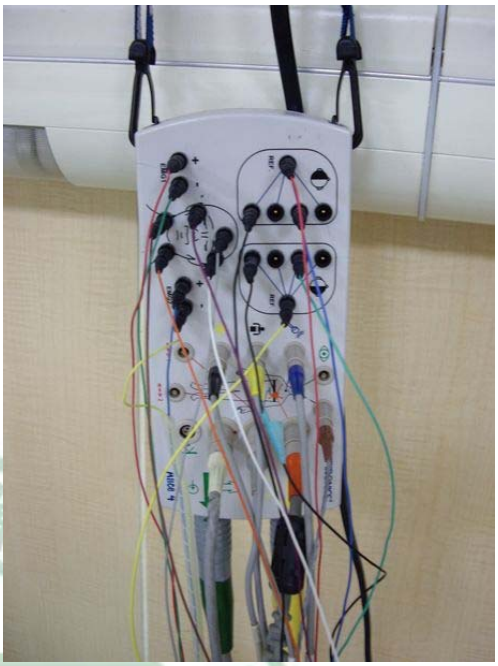

(b)

(c)

Figure 3 (a) Alice 4 System (Respironics Inc. USA); (b) patient junction box; and (c) an example showing how electrodes are placed for PSG recording in a sleep center.

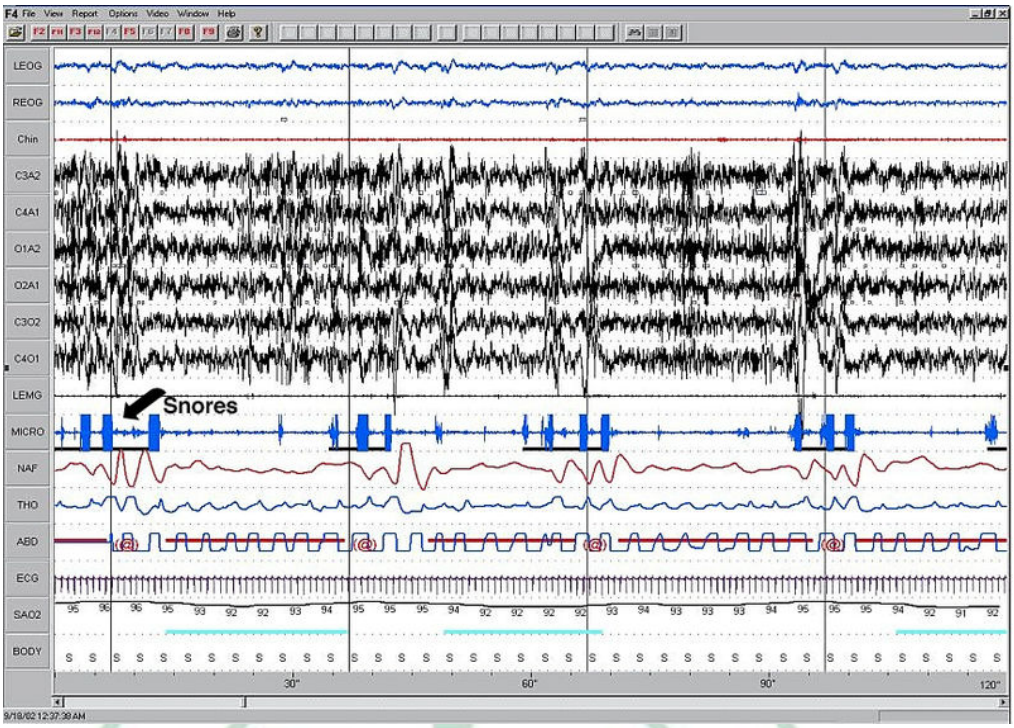

Figure 4 An example of various channels of acquired PSG signals. (Adopted from http://wikipedia.com).

1.姓名：	2.病歷號碼：	3.房間號
4.填表日期:西元　　年　　月　　日	5.性別：□男　　□女	6.生日：西元　　年　　月　　日
7.Neck circumference ：　　公分	8.BMI：	9.Waist circumference ：　　公分

以下請病患填寫，或由技術員對病患做訪問，並確認資料填寫完整：

基本資料	
9.身高：_____公分	10.體重：_____公斤
10.婚姻狀況： (1)□結婚/ 同居　(2)□分居/離婚 (3)□單身　(4)□寡居 (5)□其他：_____	11.居住地區： (1)□彰化縣市　(2)□南投縣市 (3)□台中縣市　(4)□其他：_____
11.教育程度： (0)□不識字 (1)□小學畢業或肄業　(2)□國中畢業或肄業 (3)□高中職畢業或肄業 (4)□大學專科畢業或肄業 (5)□碩士以上	12.工作狀況： (1)□失業　(2)□全職　(3)□兼職 (4)□學生　(5)□家管　(6)□退休 (7)□其他：_____
13.職業型態： (1)□非技術人員　(2)□技術人員　(3)□輪班工作 (4)□專業人員　(5)□經理管理人員 (6)□其他：_____	14.抽菸狀況： (0)□沒有　(1)□ 1-10 支/天 (2)□11-20 支/天　(3)□21-30 支/天 (4)□31 支以上/天

15.喝酒狀況： (0)□沒有 (1)□很少喝酒(過去一年 3 次(含)以內) (2)□偶而喝酒(過去一年 4-24 次/每月喝 1-2 次) (3)□經常喝酒(過去一年 25(含)次以上/每週喝酒) (4)□每天喝酒
16.通訊地址：
17.通訊電話：(日)(　)-_____ (夜)(　)-_____ (手機)_____-_____

(a)

ESS 嗜睡問卷調查

請圈選出最近一個月在以下不同情況中您打瞌睡的頻率 0：從未　1：很少　2：一半以上 3：幾乎都會 1. 坐著閱讀時 2. 看電視時 3. 在公共場合安靜坐著(如在戲院或會議中) 4. 坐車連續超過一小時(不包含自己開車) 5. 在下午躺下休息時 6. 坐著與人交談時 7. 沒有喝酒的情況下，在午餐後安靜坐著時 8. 開車中遇到交通問題，而停下數分鐘時

(b)

以下請病患填寫，或由技術員對病患做訪問，並確認資料填寫完整；

請圈選您是否有下列的症狀或發生過下列之情形？			
打鼾(打呼)	□是 □否	早上起床後覺得睡不飽	□是 □否
白天嗜睡	□是 □否	記憶問題	□是 □否
早上頭痛	□是 □否	早晨感覺口乾	□是 □否
睡覺時流口水	□是 □否	胃酸逆流	□是 □否
夢遊	□是 □否	磨牙	□是 □否
夜晚小便(一晚 2 次以上)	□是 □否	車禍(因打瞌睡所造成)	□是 □否
高血壓	□是 □否	心肌梗塞	□是 □否
糖尿病	□是 □否	心絞痛	□是 □否
高血脂	□是 □否	過敏性鼻炎	□是 □否
高尿酸	□是 □否	氣喘	□是 □否
腦中風(早上/晚上)	□是 □否	肺心症	□是 □否
腦膜出血(早上/晚上)	□是 □否	甲狀腺功能	□是 □否

(c)

Figure 5 (a) Demographic, (b) ESS, and (c) symptomatic questionnaires related to OSA diagnosis filled before PSG recording.

2.5. 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).

Tong et al. (2008) used SVM in conjunction with evolutionary information of amino acid sequences in terms of their position-specific scoring matrices to predict the RNA-binding sites. The results showed that the method has 72.2% prediction rate with 61.0% sensitivity and 83.3% specificity. The method was demonstrated to be more accurate and to have better generalization abilities when compared with previous investigations (Tong, Jiang, & Lu, 2008).

Liu et al. (2007) used SVM to analyze the tongue surface information based on hyperspectral medical tongue images. The results showed that SVM can overcome some limitations imposed by the traditional method and provide a better classification performance than the traditional method (Zhi, Zhang, Yan, Li, & Tang, 2007).

Eom et al. (2008) proposed a classifier ensemble-based method for supporting the diagnosis of cardiovascular disease (CVD). The system

combined four different classifiers, including support vector machines, neural networks, decision trees, and Bayesian networks, for CVD diagnosis. The experimental results showed that the system achieves high diagnosis accuracy (>94%), which is useful in providing clinical decision support on disease diagnosis (Eom, Kim, & Zhang, 2008).

Polat & Gunes (2007) used least-square support vector machine (LS-SVM) classifier to diagnose breast cancer. The data source of the study was Wisconsin breast cancer dataset obtained from the University of California at Irvine machine learning repository. The classification accuracy achieved 98.53% which was outstanding when compared with previous studies using other classification methods (Polat & Gunes, 2007).

Zhang et al. (2008) developed a computerized system by using SVM to distinguish cervical lymph nodes as malignant or benign on ultrasonography with a database of 210 cases. The results showed that the normalized area under the ROC curve was 0.892. Compared with the radiologist's performance (0.784), the computerized system has the potential to aid the radiologists in discriminating between malignant and benign cervical nodes (Zhang, Wang, Dong, & Wang, 2008).

The goal of SVM 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. For an example of two-class classification, the hyperplane separates two classes leaving the maximum margins from both classes is represented as (Theodoridis et al. 2003, Cristianini and Shawe-Taylor 2000):

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

The distance of a point from a hyperplane is given by

$$z = \frac{g(\mathbf{x})}{\|\mathbf{w}\|} \tag{2}$$

As shown in Fig. 6, the value of **w** and w_0 in Eq. (1) are scaled so that the values of g(x) at the nearest points in class 1 and class 2 equal to 1 and -1 respectively. Therefore, to obtain the hyperplane becomes a nonlinear quadratic optimization problem, which can be formulated as:

$$\text{Minimize } J(w) = \frac{\|\mathbf{w}\|^2}{2}, \text{ Subject to } y_i(\mathbf{w}^T\mathbf{x}_i + w_0) \geq 1, \quad i = 1,2,...,N \tag{3}$$

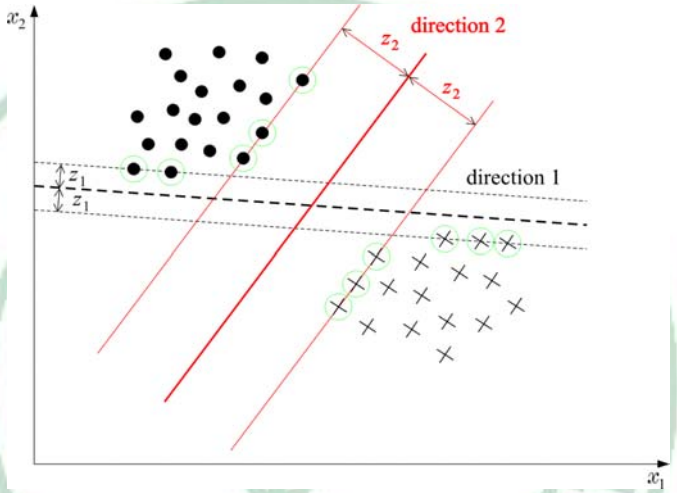

Figure 6 The hyperplane with greatest margin. Note that the margin of direction 2 is larger than the margin of direction 1 (Adopted from Theodoridis et al. 2003).

The above minimizer must satisfy Karush-Kuhn-Tucker (KKT) condition, and the problem can be solved by considering Lagrangian duality and the problem can be stated equivalently by its Wolfe dual representation form:

$$\begin{aligned} &\text{Maximize} \quad L(\mathbf{w}, w_0, \boldsymbol{\lambda}) = \frac{w^T w}{2} - \sum_{i=1}^{N} \lambda_i [y_i(\mathbf{w}^T\mathbf{x}_i + w_0) - 1] \\ &\text{Subject to} \quad \mathbf{w} = \sum_{i=1}^{N} \lambda_i y_i \mathbf{x}_i, \quad \sum_{i=1}^{N} \lambda_i y_i = 0, \quad \text{and} \quad \boldsymbol{\lambda} \geq 0 \end{aligned} \tag{4}$$

where $L(\mathbf{w}, w_0, \boldsymbol{\lambda})$ is Lagrangian function and $\boldsymbol{\lambda}$ is the vector of Lagrangian multipliers. By comparing Eqs. (3) and (4), the first two

constraints in Eq. (4) become equality constraints and make the problem easier to handle. After a little bit algebra manipulation the problem in Eq. (4) becomes

$$\max_{\lambda}(\sum_{i=1}^{N}\lambda_i - \frac{1}{2}\sum_{i,j}\lambda_i\lambda_j y_i y_j \mathbf{x}_i^T \mathbf{x}_j), \text{ Subject to } \sum_{i=1}^{N}\lambda_i y_i = 0 \text{ with } \boldsymbol{\lambda} \geq 0 \qquad \textbf{(5)}$$

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. (4).

Once the optimal hyperplane has been obtained, classification of a sample is performed based on the sign of the following equation:

$$g(\mathbf{x}) = \mathbf{w}^T\mathbf{x} + w_0 = \sum_{i=1}^{Ns}\lambda_i y_i \mathbf{x}_i^T \mathbf{x}_i + w_0 \qquad \textbf{(6)}$$

where *Ns* is the number of support vectors. For a vector $\mathbf{x}\in R_l$ in the original feature space, assume that there exists a mapping ϕ from $\mathbf{x}\in R_l$ to $y=\phi(\mathbf{x})\in R_k$., where k is usually much higher than l. Then it is always true that

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

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

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

For a nonlinear classifier, various kernels, including polynomial, radial basics function, and hyperbolic tangent, shown in Eq. (9) 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.

$$K(\mathbf{x},\mathbf{z}) = (\mathbf{x}^T\mathbf{z}+1)^q, \quad q>0 \qquad \textbf{(9a)}$$

$$K(\mathbf{x},\mathbf{z}) = \exp(-\|\mathbf{x}-\mathbf{z}\|^2/\sigma^2) \qquad \textbf{(9b)}$$

$$K(\mathbf{x},\mathbf{z}) = \tanh(\beta \mathbf{x}^T \mathbf{z} + \gamma) \quad \textbf{(9c)}$$

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.

Chapter 3 Results

3-1 Prediction of normal, mild, moderate, and severe subjects

In the first experiment, the tested subjects were divided into 4 groups based on AHI values. Table 2 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 ($5 \leqq AHI<15$), moderate ($15 \leqq AHI<30$), and severe ($30 \leqq AHI$).

Table 2. 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 2, 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.

The prediction rate (accuracy) of various OSA stages using different combinations of independent variables is shown in Tables 3. As shown in this table, although various combinations of neck circumference, BMI, ESS, and ODI have been used, applying ODI alone as the independent variable achieves highest prediction rate. This indicates that demographic information and questionnaires are not useful in elevating the predicting efficiency.

Table 3. Prediction rates of normal and three OSA stages using different combination of salient features

Fold	NC, BMI, ESS, ODI	BMI, ESS, ODI	BMI, ODI	ODI
3	70.40	71.88	71.88	73.16
4	71.51	71.51	71.88	71.69
5	71.51	71.69	71.69	72.43
6	71.69	72.43	71.69	72.43
7	72.06	71.69	71.51	72.24
8	71.32	71.88	72.06	72.24
9	72.24	72.24	72.06	72.06
10	72.23	72.43	71.52	72.61
LD	65.3%	64.7%	64.5%	63.2%

3-2 Prediction of normal and abnormal subjects

By using AHI=5 as the threshold, the subjects were divided into two groups, normal (AHI<5) and abnormal (AHI>=5). As shown in Tables 4, the successful prediction rates achieve as high as 92-93% for different combination of independent variables. Again, using only ODI as the independent variable achieves highest prediction rate, while other demographic and questionnaire variables are not helpful in improving the accuracy.

Table 4. Prediction of normal and abnormal subjects using different combination of salient features

Fold	NC, BMI, ESS, ODI	BMI, ESS, ODI	BMI, ODI	ODI
3	90.2574	91.36	90.99	93.01
4	89.3382	90.63	90.26	90.26
5	89.7059	91.36	91.36	92.10
6	90.4412	92.65	92.46	92.65
7	90.0735	91.54	90.99	92.65
8	90.0735	90.99	91.91	92.83

3-3 Prediction of severe and non-severe subjects

Here, the subjects were divided into two groups using AHI=30 as the threshold to discriminate severity of OSA; that is the subjects were classified into non-severe (AHI<30) and severe (AHI>=30) groups. As shown in Tables 5, the successful prediction rates achieve more than 90% for different combination of independent variables.

Table 5. Prediction of severe and non-severe subjects using different combination of salient features

Fold	NC, BMI, ESS, ODI	BMI, ESS, ODI	BMI, ODI	ODI
3	90.44	90.63	90.07	90.26
4	91.18	90.99	90.44	90.44
5	90.99	90.81	90.63	90.63
6	90.81	90.63	90.26	90.63
7	90.81	90.81	90.23	90.44
8	90.99	90.99	90.26	90.44

3-4 Prediction of normal, combined mild and moderate, and severe subjects

In this experiment, we intended to investigate if the normal and severe patients could be discriminated from other patients, so that they can be diagnosed using simple questionnaires and fewer PSG parameters such as

oximetry. For the prediction of normal, combined mild and moderate, and severe subject, the subjects were divided into three groups with AHI=5 and AHI=30 used as the thresholds to discriminate 3 groups including normal (AHI<5), combined mild and moderate (5<=AHI<30), and severe (AHI>=30) OSA subjects. As shown in Table 6, the successful prediction rates achieve around 82% by using ODI alone as independent variable. As expected, the prediction rate is lower than the 2-class predictions shown in Sections 3-2 and 3-3, and higher than the 4-class prediction shown in Section 3-1.

Table 6. Accuracy of using ODI as independent variable and AHI as dependent variable for predicting OSA severity.

Fold	C	gamma	CV rate	Linear discriminant
3	3	9	81.26	63.8%
4	2	8	82.80	
5	8	9	82.64	
6	2	9	82.80	
7	10	10	82.64	
8	8	8	82.80	

Figure 7(a) illustrates classification of test subjects based on AHI. In order to diagnose normal and severe subjects, the 3-class problem is divided into two 2-class problems, i.e. discriminating (1) normal from combined mild and moderate subjects and (2) severe from combined mild and moderate subjects. Regarding the first problem, the normal subjects were treated as TRUE and the combined mild and moderate as FALSE, while in the second problem the severe patients were deemed as TRUE and the combined mild and moderate as FALSE.

In Figs. 7(b) and 7(c), the numbers of true-positive, true-negative, false-positive, and false-negative of an example in discriminating the normal from combined mild and moderate and the severe from combined mild and moderate are shown, respectively. Figure 7(d) demonstrates the

sensitivity, specificity, and accuracy calculated based on this example. The mean sensitivity, specificity, and accuracy of cross validation using 4 folds in discriminating the normal and severe from the combined mild and moderate patients are depicted in Table 7.

Normal (1)	Combined Mild & Moderate (2)	Severe (3)
AHI<5	5<=AHI<30	AHI >=30

(a)

Predict / Actual	1(P)	2(N)
1(T)	14	5
2(F)	7	54

(b)

Predict / Actual	2(N)	3(P)
2(F)	54	6
3(T)	11	64

(c)

	Normal & Combined Mild and Moderate (%)	Combined Mild and Moderate & Severe (%)
Sensitivity	73.68	85.33
Specificity	88.52	90.00
Accuracy	85.00	87.41

(d)

Figure 7 (a) Illustration of dividing the suspected patients into 3 groups, i.e. normal, combined mild and moderate, and severe. An example showing the validation of the SVM model in discriminating (b) between normal and combined mild and moderate and (c) between combined mild and moderate and severe. (d) Sensitivity, specificity, and accuracy of this example. Note: T-True; F-False; P-Positive; and N-Negative.

Table 7. Mean sensitivity, specificity, and accuracy of cross validation in discriminating normal and severe from the combined mild and moderate.

	Normal & Combined Mild and Moderate (%)	Combined Mild and Moderate & Severe (%)
Sensitivity	70.39	87.20
Specificity	87.46	88.16
Accuracy	83.44	87.65

Chapter 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 helpful to increase the prediction rate. In addition, prediction accuracy using SVM is much higher than traditional linear discriminant. For example, as demonstrated in Table 6, the accuracy obtained using SVM is around 82% while it is only 64% for linear discriminant.

4.1 Cost Benefit Analysis

As shown in Table 7, for discriminating the normal from the abnormal and severe from the non-severe patients, the mean prediction rate achieves more than 83% and 88%, respectively. Additionally, the sensitivity for detecting normal subjects is only 70.39% while it reaches 87.20% for severe diagnosis. It is promising for oximetry to be used as a parameter for the diagnosis of severe patients, but not sensitive enough to detect normal patients. As shown in Table 1, the subjects tested amounts to a total of 651. Among them, 87.20% (269) of the severe patients (309) who need to be treated immediately are expected to be diagnosed based on the oximetry. The severe patients need to be treated as soon as possible. Regarding the whole population of this investigation, the percentage of severe patients is 309/651=47.47%, among them 87.20% can be detected; that is 47.47% x 87.20% = 41.39% of the total population who are suspected to have OSA can be accurately diagnosed as severe patients.

In contrast, the sensitivity in discriminating the normal from combined mild and moderate is only 70.39% using oximeter and is not sensitive enough for accurate diagnosis. The percentage of normal

subjects is 75/651=11.52%. Among them 70.39% (sensitivity) can be accurately detected; that is 11.52% x 70.39%=8.11% of the total population. Additionally, since the mean specificity is 87.46%, 12.54% of the mild and moderate patients will be diagnosed as normal using oximetry, which will seriously endanger those patients who need to be treated as soon as possible.

The sensitivity in detecting severe patients is 87.20%, which indicates that 12.80% of the subject will be treated as mild or moderate even they are severe. Further PSG test will be expected to diagnose these patients. On the other hand, the percentage of mild and moderate patients who are diagnosed as severe is 11.84% (1–specificity) which accounts to 267/651 x 11.84%= 4.86% of the total population. It is acceptable for this miss diagnosis since some investigations suggest that mild and moderate patients also need treatment using CPAP. Therefore we suggest that oximeter to be used for diagnosing severe OSA patients, but for detecting normal subjects.

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 (41.39% + 4.86%) + (480 + 4560) x (1 - 41.39% - 4.86%) = NT$2931. The cost is lower than the situation that all the subjects are examined using PSG with a saving of NT$1629 (35.72%) 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 8 compares the number and percentage of subjects with sleeping time less than and more than 4 hours threshold.

Table 8. A comparison of distribution of subjects based on length of sleeping time

Sleeping time		**Normal**	**Mild**	**Moderate**	**Severe**
<4 hr (n=85)	Number	5	7	18	55
	Percentage	5.88%	8.24%	21.18%	64.7%
≧4 hr (n=566)	Number	70	127	115	254
	Percentage	12.37%	22.44%	20.32%	44.88%
Polled (n=651)	Number	75	134	133	309
	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 9, 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 9. 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=85)	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=566)	STD	12.00	7.11	3.62	5.19	26.40	10.69	28.19
***p* value**		**.0001**	.7144	.1269	.5987	.4311	**.0042**	**.0003**

Table 10. 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=85)	STD	38.80	75.44	22.31
≧4 hr	Mean	16.52	163.11	33.19
(n=566)	STD	14.41	102.26	20.53
***p* value**		**.0001**	**.0001**	**.0042**

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 10, 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.

With regard to the second possibility, the data collected from the 85 subjects who had sleeping time less than 4 hours were removed and resulted in a total of 566 subjects for further analysis. The percentage of patients without enough sleeping time accounts to 13.06%. Table 11 shows the mean sensitivity, specificity, and accuracy in discriminating the normal subjects and severe patients from the combined mild and moderate group. To compare Table 11 with Table 7, only little change is observed. The influence of patients whose sleeping time less than 4 hours needs to be further investigated.

Table 11. Mean sensitivity, specificity, and accuracy of cross validation in discriminating normal and severe from the combined mild and moderate for subjects whose sleeping time is more than 4 hours.

	Normal & Combined Mild and Moderate (%)	Combined Mild and Moderate & Severe (%)
Sensitivity	77.42	84.24
Specificity	87.23	89.67
Accuracy	84.90	86.74

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.

Chapter 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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