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血液透析病人睡眠品質及影響因素探討

Quality of Sleep and the Affecting Factors in ESRD Patients with Hemodialysis in Taiwan

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摘要

目的：評估台灣血液透析病人，其睡眠品質不良的發生率，了解腿部不寧及憂鬱對睡眠品質的影響，分析睡眠品質良好與不好的病人，其基本特質、臨床因素等的差異。

方法：以台灣血液透析病人為母群體，以 63 個透析中心，經系統性隨機選擇 348 個血液透析病人，以匹茲堡睡眠品質量表測量睡眠品質為依變項，以國際腿部不寧量表測量腿部不寧徵候群症狀嚴重度，貝克憂鬱量表測量憂鬱嚴重度。以病人特質、合併疾病、臨床因素、憂鬱、腿部不寧徵候群症狀為變項。使用複迴歸探討影響睡眠品質相關因素。

結果：透析病人抱怨睡眠品質不良的發生率為 66%。調整其它變項後，以複迴歸分析，發現睡眠品質不良與年齡、家庭收入、使用助眠藥物、腿部不寧的嚴重度、憂鬱有顯著關聯性($P<0.05$)，其中憂鬱症狀愈嚴重的病人，睡眠品質愈差。

結論： 睡眠品質不良是血液透析病人常見的問題，腿部不寧、憂鬱會降低血液透析病人睡眠品質，早期發現腿部不寧徵候群及憂鬱，早期診斷及治療是未來血液透析醫療應努力的方向及課題。

關鍵字：睡眠品質、血液透析、憂鬱、腿部不寧

Abstract

Objectives: The aim of this study was to determine the prevalence of poor quality of sleep (QOS) and the affecting factors in patients on maintenance hemodialysis in Taiwan.

Methods: This study population was 44,121 HD patients in Taiwan. A total of 348 hemodialysis patients by systematic random selection in 63 hemodialysis units were enrolled in the cross-sectional study. We used Pittsburgh Sleep Quality Index (PSQI) to measure the quality of sleep (QOS) as dependent variable. The Beck Depression Inventory (BDI)-II Chinese version was used to rate the severity of depressive symptoms. We used International Restless Legs Syndrome Rating Scale (IRLS) to illustrate the severity of restless legs syndrome (RLS). The demographics, co-morbidity, hemodialysis (HD) mode, clinical parameters, the severity of depressive symptoms, and the severity of RLS are independent variables. We analyzed the categorical variables by the chi-square test or the Fisher exact test and continuous variables by student's t-test. We use multiple linear regression analysis to estimate the relationship between the QOS and independent variables.

Results: The prevalence of sleep complaints in Taiwanese HD patients was 66%. Subjects characterized by poor QOS were significantly more likely to be female, lower education status, without work, sleep medicine, RLS, and depression (all $p<0.05$). QOS was significantly associated with age, family income, sleep medicine, RLS, and depression by multiple linear regression after controlling for the other variables (all $p<0.05$).

Conclusions: Age, less family income, usage of sleep medicine, RLS symptom, and depression are independently associated with poor QOS in HD patients. To find out depression and RLS of HD patients as early as possible is important.

Keywords: quality of sleep, hemodialysis, depression, restless legs syndrome

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Chapter 1 Introduction

Session 1 Background

End-stage renal disease (ESRD) is one of the most important health problems in Taiwan. The major leading causes of ESRD in Taiwan are diabetic mellitus (DM), chronic glomerulonephritis (CGN) and hypertension (HT) [1]. Diabetic nephropathy is getting more and more proportion in new cases of treated ESRD from 2001(37.7%), 2002(39.7%), to 2003(42.2%) in our country [2]. As same as United States, according to the United States Renal Data System (USRDS), the proportion of DM in new cases of treated ESRD was approximately 44% in 2002 [3]. The overall crude annual prevalence rate of maintaining dialysis for ESRD was 400 per million populations in our country in 2003 [2]. In 2003, nephritis, nephrotic syndrome and nephrosis ranked eighth in the leading cause of death in Taiwan area [4]. By the end of March in 2005, there were 46,512 patients with ESRD on dialysis in this country and over 93.4% under hemodialysis (HD) therapy [5]. In 2003, the total direct expenditures for dialysis patients from Bureau of National Health Insurance (BNHI) was over NT$ 21 billions, and it is the most usage of expenditures in single disease from BNHI [6].

Session 2 Statements of Problems

According to the increase of prevalence and cost of treatment in ESRD, the physicians and researchers put emphasis on improving clinical outcomes, such as issue of hospitalization, morbidity and mortality. The National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) sets

guidelines to care the patients under dialysis, such as, guidelines for cardiovascular disease, anemia, HD adequacy, vascular access, and nutrition [7]. These guidelines achieved the substantial improvement in the qualities and outcomes of medical care for ESRD patients. The data of USRDS revealed that the first year death rates for dialysis patients was declined from about 35-38% to 25.7% from 1983 through 1993 [8]. Many data analysis from the USRDS and studies reported the lower hospitalization, morbidity and mortality after medical interventions [8, 9, 10, 11]. The dialysis dosage, usage of synthetic membranes and erythropoietin played important roles in decrease of mortality. After the clinical outcomes improved, the clinical and research settings have paid more attention to the quality of life in patients treated with dialysis. Quality of sleep (QOS) is one of the most important indicators of quality of life because its important impact on healthy condition [12, 13, 14]. To gain more complete knowledge of QOS and the affecting factors in HD patients is absolutely imperative if our efforts are going to ameliorate the health outcome.

The incidence of subjective sleep disturbance has been demonstrated over 50% to 80% in ESRD patients surveyed by many studies [12, 13, 14, 15]. Sleep apnea syndrome (SAS), periodic limb movement disorder (PLMD), and restless legs syndrome (RLS) had also been documented higher prevalent rate than the general population [16, 17, 18]. There is little report about QOS in these groups in Taiwan. Hui et al. reported the prevalence rate of subjective sleep complaints is 52% in peritoneal dialysis (PD) patients in Taipei [13]. They found that 18 (52%) of a sample size of 34 patients who completed the survey described sleep complaints. Another study by Tsay et al. reported that the QOS in HD patients after acupoints massage was improved [19]. These patients were all limited in north Taiwan. To our knowledge, there is no large-scale survey about QOS in ESRD patients treated with

maintenance HD in Taiwan. However, fewer studies discuss QOS and the affecting factors in ESRD patients treated with maintenance HD in our country.

Session 3 Research Objectives

1. Describe demographics, co-morbidity, clinical parameters, depression level, restless legs syndrome in HD patients. Using the descriptive analysis, this study wants to determine the demographics, co-morbidity, and clinical data of enrolled HD patients.
2. Assess the level of depression symptom, restless legs syndrome, and QOS in HD patients. Using the Beck Depression Inventory II of Chinese version, the International Restless Legs Syndrome rating scale, and the Pittsburgh Sleep Quality Index, this study measures the level of depression symptom, restless legs syndrome, and QOS in samples from HD facilities participating in this study.
3. Determine the statistic differences between poor and good quality of sleep in patients under this study with demographics, co-morbidity, clinical parameters, depression levels, restless legs syndrome scale.

   Using multiple linear regression analysis, this study aims to determine the factors associated with the poor QOS in HD patients.

Chapter 2 Literature Review

Session 1 Uremia and Dialysis

1. Renal Function

The major functions of the kidney can be briefly classified as follows:

1. To excrete the metabolic end products and solutes. The kidneys are the major organ to excrete the protein products, the urea, creatinine, etc. As we know, most drugs are excreted in unchanged form by kidney.

2. To adjust the body fluid and electrolytes and keep body component steadily. The secretion and reabsorption of water and electrolyte in different parts of the renal tubules play the central role in this mechanism.

3. To produce hormone and activate hormone. Erythropoietin is produced by renal interstitial cell to stimulate erythrocyte production in bone marrow. Renin is secreted by the juxtaglomerular cells and initiates a sequence reaction in regulation of blood pressure. Active form of vitamin D3 is formed by renal tubule cell and its role is to regulate the calcium and phosphate.

2. Chronic Kidney Diseases (CKD)

In America, there are twenty million adults have CKD, about 1 person in 9 adults [7]. Chronic renal failure is a term that includes a large number of progressive processes of renal destruction. It is characterized by gradual loss of renal function. The major deteriorations of function in chronic renal failure are related to the decrease of glomerular filtration rate and the loss of tubular functions. The result was the accumulation of the waste, such as blood urea nitrogen and creatinine. Furthermore, the impairment of endocrine activity, such as erythropoietin secretion,

may provide the clinical presentations of chronic renal failure.

The statistical data in 2002 from USRDS, diabetes was the first leading cause of new ESRD patients, followed by hypertension, glomerulonephritis and cystic kidney [8]. But in Taiwan, the first leading cause of new ESRD cases was still glomerulonephritis (44%), followed by diabetes (25.2%), hypertension (6.7%), and chronic interstitial nephritis (3.4%) in 2001 [20]. After 2002, the situation was changed. Glomerulonephritis replaced by diabetes, the proportion of diabetes in new ESRD cases was from 39.7% (2002) to 42.2% (2003). Diabetes plays more important role in the new ESRD cases in our country [2].

NKF-K/DOQI guidelines defined that CKD should be established based on follow conditions: 1. The presences of kidney damage greater than or equal to three months was based on structure or functional abnormalities or markers of kidney damage. 2. The level of kidney function or glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 was persisted for greater than or equal to three months. The stages of CKD are expression of functional abnormality by the level of GFR, with lower stage representing higher GFR levels, as follows [7]:

Stage 1. Individual has kidney damage with normal or increase GFR. GFR is greater than or equal to 90 mL/min/1.73 m^2.

Stage 2. Individual has kidney damage with mild decrease GFR. GFR is between 60 to 89 mL/min/1.73 m^2.

Stage 3. Individual has kidney damage with moderate decrease GFR. GFR is between 30 to 59 mL/min/1.73 m^2.

Stage 4. Individual has kidney damage with severe decrease GFR. GFR is between 15 to 29 mL/min/1.73 m^2.

Stage 5. Individual has kidney damage with marked decrease GFR. GFR is less than 15 mL/min/1.73 m^2.

All the patients with kidney damage greater than or equal to three months must be detective and intervened as early as possible to prevent renal function progressively going down to ESRD. Generally speaking, renal replacement therapy is expected when individual with chronic kidney disease in stage 4 or 5 even if many medical efforts have been done. Clinically, chronic kidney disease often appears without any symptom and sign until renal damage is widely enough to 80-90% loss of nephrons.

3. ESRD and Uremia

ESRD is an administrative term definite almost whole failure of kidneys' function to do their job in the body. It commonly occurs when the GFR is less than 10 mL/min/1.73 m^2 with or without symptom and sign. In this condition, renal replacement therapy or kidney transplant is necessary due to the accumulation of waste and metabolic poisoning products in the body at the point of renal function.

Uremia is a clinical term that means "urine in the blood". It does not demonstrate the uremic syndrome entirely accurate but it presents progressive accumulation of toxic products from dietary and endogenous derivations. Chronic kidney failure is often in symptom-free condition until the serum creatinine increases over 6-10 mg/dl. Abnormalities of laboratory finding appear long before any symptoms presented. Significant symptoms and physical manifestations appear lately in the course. The native kidneys have greatly reserved function but also because the residual nephrons have a noteworthy capacity to compensate the loss of other nephrons. The first symptoms may be influenza-like presentation, general malaise, fatigue, headache, and inability to concentrate. Loss of appetite, altered taste sensation with body weight loss may occur early in gastrointestinal symptom. The skin pigmentation increased after sunlight exposure. Extracellular volume

expansion resulted in severe lower leg edema, pleural effusion, and ascites [21].

The major symptoms and signs of uremia are related to three aspects of function: diminished excretion of water and electrolytes; declined excretion of the metabolic end products and solutes (also called uremic toxins); reduced renal hormone synthesis. The stage 4 or 5 of chronic kidney diseases always progress, the uremic syndrome can be predicted but the first appearance is usually nonspecific. Important manifestations of the uremic syndrome are listed in Table 2-1 [21].

Restrictive diet with low protein content is the most important prescription to patient with uremic syndrome that rejects dialysis. It is known for improving the symptoms such as anorexia, nausea, vomiting, lethargy, and somnolence. Early studies provide evidence of that protein derivatives are major factors related to uremic syndrome [22]. In uremic patients, many substances accumulated in the body that could be potentially toxic compounds are listed in Table 2-2 [21]. The cumulative effect of uremic toxins leads into multiple organs dysfunction. As syndrome depicted in Table 2-1, the initiation of renal replacement therapy is need for the debilitating health of patient.

In Taiwan, ESRD patients need to apply the uremic major illness card (UMIC) from Bureau of National Health Insurance (BNHI) for initiation and maintenance dialysis if the payment from BNHI [23]. The absolute criteria to apply the UMIC are 24 hours creatinine clearance rate (CCR) is less than 5 ml/minute or plasma creatinine is greater than 8 mg/dl. Individual with ESRD, however, the 24 hours CCR is less than 15 ml/minute or plasma creatinine is greater than 6 mg/dl with following symptoms- heart failure or pulmonary edema, pericarditis, bleeding tendency, neurological abnormalities, hyperkalemia, severe metabolic acidosis, intractable nausea and vomiting, cachexia, and severe azotemia (blood urea nitrogen greater than 100 mg/dl) can also apply the UMIC to maintain dialysis.

4. Hemodialysis

The term “Dialysis” was first described by Thomas Graham (1805-1869), he made a loop dialyzer membrane and found that process of the some crystalloids pass through the semipermeable membrane and colloids cannot pass through the membrane. He can be called the father of modern dialysis [24]. In 1945, Willem Kolff performed the first clinically successful hemodialysis in a patient with renal failure on comatose stage in Netherlands [24]. The hemodialysis is performed through diffusion and ultrafiltration which needs a semipermeable membrane with solute-discriminatory to separate the blood from dialysate. Small solutes, such as urea and electrolytes, pass easily through the membrane. It is more difficult for larger solutes to pass through the membrane than small solutes. The hemodialytic machine is used to generate negative hydraulic pressure on the dialysate side to drive ultrafiltration. Therefore, the major elements of hemodialysis are 1) artificial kidney or dialyzer; 2) machine to drive ultrafiltration and pump the dialysate and patient’s blood through the dialyzer; 3) the dialysate, that is the liquid with adjusted chemical composition used for solute clearance. The dialysate and patient’s blood are pumped along the dialyzer in contrary direction at flow rate of 500 and 200 to 400 mL/min. The flow rate is chose by physician’s decision under consideration of patient’s status and the major factors affecting the effectiveness of the hemodialysis.

There are so many kinds of commercial artificial kidney- such as modified biologic materials or synthetic materials- used in renal replacement therapy. The major consideration in choice of dialyzer is made by its ability to clear the toxin particles and its potential for water removal. Its biocompatibility after contacting the blood and the static volume are also the consideration in decision-making. Another weight in the physician’s mind is the reprocessing probability and cost. In general, most dialyzers used in Taiwan are synthetic membranes because of more

biocompatibility.

The solute concentration gradients started the diffusion process across the dialyzer by dialysate compositions. It is important to keep dialysate sodium concentrations similar to serum to prevent sodium imbalance and hemolysis. The dialysate potassium concentration is often kept in 0-4 meq/Liter since most of the ESRD patient impaired the ability to secrete potassium. The other components are glucose, bicarbonate, calcium, magnesium, and chloride. All of the elements are formulated commercially in powder or liquid form. The liquid dialysate with fixed formulation can be used immediately after opened. A reconstituted dialysate is supplied by powdered concentrate that is diluted with purified water processed by reverse osmosis device, ion exchange, water softener, carbon adsorption and filters.

The blood and dialysate are pumped by dialysis machine to create negative pressure in dialysate side between dialyzer. The dialysis machine needs to mix liquid dialysate with purified water to appropriate composition, to keep adequate dialysate temperature, to maintain blood and dialysate flow for ultrafiltration, and to monitor air bubbles in blood and blood leakage in dialysate. It is important to keep alertly monitoring above parameters during dialysis session to prevent lethal event.

The therapies of ESRD are dialysis and kidney transplantation. The patients should be fully informed of the services available to them, including PD, HD, and transplantation. In Taiwan, most of patients (93.4%) selected HD and received dialysis in facility of hospitals or clinics [5]. Long-term vascular access for HD is ordinarily established by arteriovenous (AV) fistula creation in the upper extremities after patient's selection of HD. AV fistula needs 4-8 weeks to mature (wall thickened and lumen dilatation by blood flow). After AV fistula punctured with two needles and connected with blood tube to the dialyzer and dialysis machine, dialysis is starting. The blood exposes to the extracorporeal circuit and

needs anticoagulant to prevent the clotting mechanism.

Session 2 Outcome of ESRD Therapy

The outcome of therapy is the major concerning decision in selection of a treatment by patient and his or her physician. There are many studies in ESRD patients which are around the outcome of therapy; such as to improve the survival rate, decrease the hospitalization rate, ameliorate the quality of life, return to work or social activity or schooling (9,10,16,18). There are many subjects to evaluate the outcome of ESRD therapy; such as mortality, morbidity, quality of life and rehabilitation.

1. Mortality

The number of deaths in a year as a percentage of the mean of the number of ESRD patients at the beginning and end of the year is the crude mortality rate. It is not a good method for matching patients in different treatment due to individual variant, financial condition, social supports, and not all patients have died under analytic time. Kaplan-Meier (K-M) estimation is the most commonly used method to depict survival curves in ESRD patients [16, 25]. Time sequence in beginning of follow–up is depicted on the horizontal axis, and the percentage or probability of patients alive at a definite time is depicted on the vertical axis. Mortality is one of the most important and most commonly used methods to describe outcome for ESRD patients. USRDS points out that the adjusted one-year mortality rate of patients in United State is reduced gradually from 35-40% in 1985 to 22-25% in 2002 [26]. In 2001, there are 1019 (3%) patients on maintenance HD over 15 years, 10.2% patients between 10-15 years, and 24.6% patients between 5-10 years in

Taiwan [20].

The most important factors affecting mortality rate are age, race, cause of ESRD, pre-existing cardiac disease, gender, anemia, dialysis adequacy, co-morbidity [8,26]. The risk factors of mortality are smoking, neoplasm, malnutrition, and low serum albumin [8,26]. The leading causes of death in dialysis patients in Taiwan are cardiopulmonary system diseases (24.3%), and followed by infectious diseases (14.9%), neoplasm (4.6%), central nervous system diseases (4.5%), and gastrointestinal diseases (4.5%) [20].

Another complex method of survival analysis uses a multiple regression model, the most known of which is the Cox proportional hazards regression model. It is used to estimate the effects on mortality rate of different factors simultaneously or patients in different group [27]

.

2. Hospitalization

Hospitalization is one of the representatives of the healthy condition for ESRD patient. It is difficult to compare between countries because many factors such as culture, geographic differences, health insurance status, and political rules. It can be accumulated in hospitalization rate such as Point-prevalent sample or Period-prevalent sample over a year period, numbers of admissions, and length of hospital stay per year. A large-scale study in five European countries participating in the Dialysis Outcomes and Practice Pattern Study (DOPPS) reported that hospitalization rate was 0.99 per patient year and the mean length of hospital stay was 11 days. The major causes of hospitalization were cardiovascular-related diseases, vascular access-related diseases, infectious diseases, gastrointestinal diseases, and liver-related diseases [28].

Hospitalization data is reported annually in the USRDS, including times of

admissions and hospital days per year. Statistic data of hospitalization can be used to compare in diabetics and non-diabetics patients, HD and CAPD patients, and cause of ESRD and with treatment modality. In all age groups, the hospitalization rates for diabetics are higher than those for non-diabetics. The most common discharge diagnoses are cardiovascular diseases, infectious diseases, and gastrointestinal diseases [26].

3. Rehabilitation

Rehabilitation is a surrogate of the fundamental base of social life and ability to return to work or school. It has always been of concern in ESRD patients for going back to normal life as early as possible. The need of active patient participation is important to return functional activity. Psychologic support by family and friend can partially motivate the sense of controlling themselves health and desire of social activity. The rehabilitation of ESRD patients in Taiwan is household (23%), full time job (10.5%), part time job (6.7%), school (0.5%), unemployed (3.4%), self-care but need help (13.6%), and bed-ridden (11.5%) [20].

4. Quality of Life (QOL)

The World Health Organization (WHO) put forward a definition of quality of life (QOL) in 1993. It is defined as " An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [29]. In other word, QOL describes how well people feel about their life in many aspects as following: physical, psychological, social, and economic.

In ESRD patients on dialysis therapy, better survival rate were ascribed to aggressive medical care, new technology, and social supports [30,31]. Now, the goal

of health care is not only to prolong the life or to ameliorate disease but also in improving the QOL. Therefore, QOL is the important indicator of the evaluation of therapy and health care.

QOL can be measured from many aspects with subjective indicators in field such as physical function, energy, psychological function, social activity, life satisfaction, sexual function, happiness, and individual values.

Objective assessments of QOL contain functional ability, employment status, and health status. For example, the ways to quantify a person's ability to perform the test in observed variables such as muscle strength, speed of contraction and balance are good examinations in functional ability. The indicator which often used to estimate the functional ability of the ESRD patients is Karnofsky index. In Taiwan, the HD quality analysis in ESRD patients revealed that the Karnofsky score in most of patients are shown in Table 2-3 [20].

Employment is evaluated by employed or not under the condition of patient's perception of himself or herself assessment with having ability to work.

Another objective measure is the established generic Sickness Impact Profile to assess health status of disability related with chronic illness [32]. It can be used to check a person's ability to do daily work, such as shopping, housework, and to evaluate the change in memory and judgment behavior.

There are many subjective measures includes medical outcome study such as the World Health Organization Quality of life (WHOQOL) assessment instrument, Short Form-36 (SF-36) health survey, and the Kidney Disease Quality of life (KDQOL) instrument [29,33,34]. A total randomly selected sample size with 17236 HD patients in a cross-national prospective, observational study used KDQOL in 7 countries (USA, Japan, France, Germany, Italy, Spain, and the United Kingdom) revealed that QOL were highly related to risk of death and hospitalization in HD

patients under adjustment of demographic and co-morbid factors [35]. This large-scale study revealed that QOL was affected by socioeconomic factors (income, education, occupational status, and living status), treatment modal, laboratory factors, and co-morbidity factors. The living status, sleep especially affects QOL in ESRD patient on maintaining HD.

Session 3 Quality of Sleep (QOS)

To maintain healthy circadian rhythm of sleep and waking is an important element of life cycle. It is very common to complaint sleep problems from ESRD patients. In clinical setting, a lot of burdens were borne by sleep disturbance in ESRD patients. There is a battery of reports about sleep disturbances in HD patients. A very high prevalence of subjective sleep complaints has been reported by over 50-80% of patients surveyed [12, 13, 14, 15, 16, 17, 19]. ESRD directly affected QOS, and therefore impacted the QOL [15]. Performing a more complete comprehending the sleep problems occurred by HD patients is important if developing better health outcomes is the object.

1. Sleep Disturbances in Dialysis Patients

Sleep problems are always existence from general population to ESRD patients. Daly and Hassall reported one of the earliest studies about sleep problem in 34 HD patients in 1970 [36]. It was noted that patients slept less on nights following dialysis. Total sleep time is apparently deceased and poor recovery of physical energy. Strub et al in their analysis illustrated that 63% of a sample of 22 HD patients reported subjective sleep disturbance represented by diminished sleep efficiency, portioned sleep, and more time lying awake in bed [37]. This was one of the earliest studies reported the prevalence of sleep complaints in HD patients. They

found that there was no difference in age, personality, or medications between subjects with sleep symptoms and those without. The limits of this study were small sample size and without controlling variables that affect sleep quality.

In 1992, Holly et al. assessed the prevalence of 48 HD patients, 22 peritoneal dialysis (PD) patients, and 41 control subjects [12]. Fifty-two percent of HD, 50% of PD and 12% of control subjects reported sleeping problems. Caffeine intake and worry were associated with sleep disturbance. The same authors reported that jerking legs (28%), trouble falling asleep (67%), early morning waking (72%), nighttime waking (80%), and restless legs (83%) were the major complaints by HD patients [38]. The prevalence of self-reported sleep complaints was equal in HD and PD patients in this study. Walker et al. [14] described the extent, severity, and types of subjective sleep disturbance with a sleep questionnaire in a 64 HD patients units. Fifty-four patients completed the survey and 83% of subjects had sleep-wake complaints. The most common complaints included daytime sleepiness (66.7%), daily naps (59.2%), restless leg syndrome (RLS) (57.4%), disturbed sleep (51.8%), and use of sleeping medication (46.3%). Twenty-eight patients reported disturbed sleep characterized by delayed sleep onset, frequent awakening, RLS causing disturbed sleep, or generalized restlessness during the night. Their data revealed that RLS had an association with levels of urea and creatinine. Another complaint was often claimed to clinical team by HD patients. Which was daily sleepiness. In 1994, a study reported trouble sleeping and daily sleepiness were highly ranked in the KDQOL bothersome symptoms in HD patients from 9 different outpatient dialysis center located in California [34].

Winkelman et al. [39] designed a study to investigate the incidence of RLS in HD patients and to identify associated factors in 1996. They studied 204 HD patients with questionnaire about symptoms of RLS, sleep habits, pruritus, and

adherence to dialysis therapy. The study used 129 patients with heart disease as control group. ESRD patients received laboratory tests and sensory nerve amplitudes recorded. Twenty percent of the HD patients and 6 % of the control subjects reported moderate to severe RLS. Sleep onset with delay and reduction of total sleep time in HD patients compared to control group. RLS were correlated with sleep measures and pruritus. Sleep complaints included nocturnal awakening, sleep onset latency, total sleep time diminished, use of sleep medications, and nocturnal leg movement. They found increased mortality in patients with RLS at a 2.5-year follow-up.

Benz et al. conducted a study to investigate predictors of mortality with reviewed the medical record in twenty-nine ESRD patients who had previously undergone polysomnography (PSG) between 1990 and 1993 [16]. They examine the associated between periodic limb movements (PLMS) in sleep and mortality in ESRD. Post 48 months follow-up, the patients with a PLMS index less than 20 had high mortality than patients with a PLMS index of 20 or greater. After controlling for the other risk factors, such as, urea reduction rate, albumin level, and hematocrit, comparing patients having greater PLMS index with patients having less PLMS index in survival rate still reached statistical significance. This study reported the potentially new predictors of mortality in ESRD patients with sleep disorders.

Sakami et al examined insomnia and the affecting effect on immune functions in 578 Japanese men without any toxic exposure [40]. The study found the prevalence of insomnia in 9.2% Japanese men. The insomniac men without any medical disorders had significantly lower interferon-gamma and ratio of interferon-gamma to interleukin –4 than non-insomniac men. A significantly lower interferon-gamma to interleukin-4 ratio was detected in men with insufficient sleep or difficulty initiating sleep. They conclude that the immune system could be negatively affected

by sleep quality in insomnia. In 2005, Erten et al. reported the similar finding that lower interleukin-6 and tumor necrosis factor-alpha was got in obstructive sleep apnea patients in maintenance HD with sleep complaints [41]

Olson et al. reported a study with questionnaire in 441 subjects age 34 to 69 years old from a community to measure the association between sleep-disordered breathing (SDB) in 1995 [42]. The hypertension, coronary artery disease, and occlusive vascular disease diagnosed by physician. They found that the prevalence of hypertension, coronary artery disease, and occlusive vascular disease were significantly increased in the subjects with SDB. Hanly and Pierratos found the mean serum creatinine was lower and higher mean serum bicarbonate in patients with nocturnal HD 8 hours during six or seven nights a week than same patients on conventional HD for 4 hours on each of three days per week [43]. There was significantly reduction in sleep apnea-hypopnea index from polysomnography study compared nocturnal HD with conventional HD. In 2001, the Framingham Heart Study matched the age, sex, and body mass index from subjects with polysomnography survey. Ninety subjects with SDB defined as a respiratory disturbance index (RDI) score > 90 percentile were compared with 90 low-RDI subjects [44]. Right ventricular wall thickness was significantly increased in subjects with SDB. Zoccali et al. [45] found sleep apnea inducing nocturnal hypoxemia, after that they recorded cardiovascular events during follow-up. They excluded patients on regular HD with primary sleep apnea, pulmonary diseases, and illness causing sleep apnea. The study found that the risk of cardiovascular increased 33 % in 1 % decrease in average nocturnal oxygen saturation.

In Italy, Sabbatini et al. organized a study that aimed to investigate sleep disturbances in 694 HD patients in 21 different HD units in Naples and its neighborhood with a specific questionnaire in 2002 [46]. In this study, the

prevalence of the HD patients with sleep disturbances was 86%. There was a significantly higher sleep disturbance in HD patients on dialysis greater than 12 months than patients on dialysis less than 12 months. The patients dialyzed in the morning were in higher risk of insomnia than patients dialyzed in the afternoon. There was a significant difference in parathyroid hormone, pre-dialysis plasma values of creatinine and urea in the insomnia group compared with control group.

Mucsi et al. designed a cross-sectional study to assess the prevalence of sleep problems and examined their effect on quality of life in Hungary [47]. Their data revealed that 65% of the patients had at least one sleep disorder. The first sleep complaint was insomnia in 49% of patients. The prevalence of patients with sleep apnea syndrome was 32%. The prevalence of patients with RLS was 15 %. They concluded that sleep disorders was correlated to illness intrusiveness, a significant factor of health-related quality of life. Another cross-sectional study reported by Mucsi et al. in 2005 [17], the aim of the study was to investigate the relationship of RLS, insomnia and specific insomnia symptoms with health-related QOL in 333 HD patients. The prevalence of RLS was 14%. There were higher co-morbidity in patients with than without RLS. RLS was associated with impaired overall QOS and poorer QOL. Parker et al. designed a study with objective polysomnography measures to compare chronic kidney disease (CKD) patients with estimated GFR of 14.5 ml/min and HD patients with Kt/V > 1.2 (equivalent to GFR of 10-15 ml/min) [48]. They reported that the total sleep time and sleep efficiency were both reduced in chronic kidney disease patients without dialysis and HD patients in 2005. More wake after sleep onset, much periodic limb movement, longer sleep latency, lower efficiency in sleep, and less sleep time were also found in comparing HD group to CKD group. After matching the metabolic data in both groups, they suggested that the sleep problems of both groups might have different etiologies. The etiologies of

sleep disturbances in CKD patients might be due to functional and psychological factors. The sleep disturbances in HD patients might be due to intrinsic sleep disruption (arousals, apnoeas and limb movements).

Merlino et al. conducted a study to assess the prevalence of sleep disorders using a self-administered questionnaire in 883 ESRD patients in Italy [49]. The record included the demographic, lifestyle, clinical and laboratory data. The percentage of insomnia, RLS, sleep apnea syndrome, nightmares and excessive daytime sleepiness were 69.1%, 18.4%, 23.6%, 13.3% and 11.8%. The data revealed 80% of patients with at least one sleep disorder. The risk factors were older age, excessive alcohol intake, smoking, polyneuropathy and dialysis in the morning.

2. The factors influence sleep disturbance in HD patients

The etiologies of sleep disturbance in ESRD patients on maintaining HD are often multiple factors. Parker summarized the relevant factors to influence sleep disturbance in HD patients, such as disease-related factors, psychological factors, treatment-related factors, lifestyle factors, and demographic factors. (Figure 2-1) [50].

QOS in ESRD patients is an important issue confirmed by clinicians and researchers. QOS in ESRD patients includes the quantitative and qualitative aspects of sleep, it is rather subjective and variable between individuals. However, the QOS consists many of components. It is difficult to define and measure objectively due to complex aspects. Furthermore, QOS assessed outcome may be changing by subjective perceiving in quality. Finally, sleep quality measuring is influenced by study's architectural design.

There are a lot of evidences link diseases and sleep disorder [12, 51, 52, 53], such as cardiovascular disease, rheumatoid arthritis, fibromyalgia, asthma, chronic obstructive pulmonary disease, hyperparathyrodism, and gastroesophageal reflux.

The hypertension, coronary artery disease, claudication, and stroke are significantly correlated sleep disturbance in HD patients [42]. Uremic patients with hyperparathyrodism or pruritus complaint sleep problem [12, 39, 46].

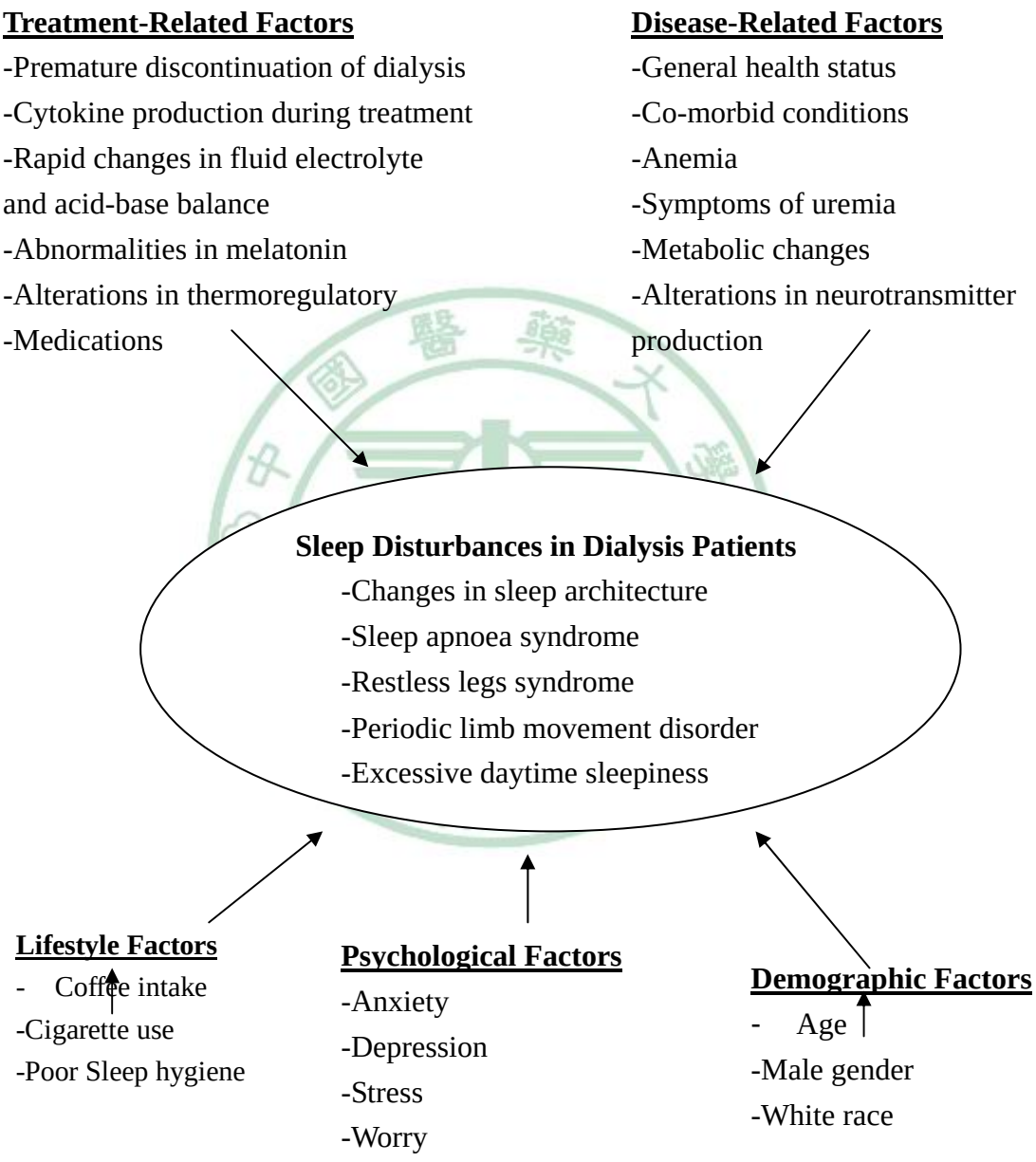

Figure 2-1. Factors potentially contributing to sleep disturbances in dialysis patients.

Source: Parker KP. Sleep disturbances in dialysis patients. Sleep Med Rev. 2003; 7(2):131-43.

The most frequent psychological problems affecting sleep disturbances include depression, anxiety, stress, and worry in general population. Worry was found to associate reported sleep disturbances in patients under dialysis[12]. In 2002, Williams et al reported a large-population study (The Kidney Outcomes Prediction and Evaluation Study, KOPE) to identify the correlation between sleep disturbances and psychosocial problems [54]. There was significantly associated in higher levels of depressive symptom with sleep disturbance. HD patients with greater levels of anxiety had poor sleep behavior than HD patients without. Especially, the patients have been in trouble falling asleep and feeling tired in the morning. The similar relationship between anxiety, worry, and sleep disorders was reported in Hong Kong Chinese patients [55]. A study from Japan reported that the anxiety and emotion-oriented coping stress were significantly associated with restless leg syndrome in ESRD patients [56]. In 2005, Wuerth et al. reported that the estimated prevalence of depression in ESRD patients was 20-30% [57]. They surveyed 380 PD patients for depression with BDI. There was 49% of patients who had a BDI score of 11 or greater than 11. Eighteen percent of the patients received pharmacologic therapy and BDI score improved from mean 17.4 to 8.4 point.

Soldatos et al. reported that cigarette smoking contributed difficult falling asleep and increasing total time awake in 1980 [58]. The similar effect was reported in ESRD patients [12, 49]. Holley et al. and Walker et al. reported that caffeine drinking was associated with sleep problem [12, 14]. The other lifestyle factors influenced sleep disturbances was alcohol consumption [49]. The report from Hong Kong did not revealed the similar effect of alcohol and caffeine drinking in Chinese ESRD patients in continuous ambulatory peritoneal dialysis [55].

In human being, aging is a nature process and the length of sleep gradually decreased. There were reports that aging was the risk factors to sleep problems in

ESRD patients [14, 49, 59], but one report indicated no relation between age and sleep disturbances [12]. Male adult was associated with more sleep disturbances in ESRD patients [14, 60], even in pediatric dialysis patients [61]. More sleep complaints in white race had also been reported [59]. The clinical parameters influencing sleep disturbances in ESRD patients include blood urea nitrogen (BUN), creatinine [16, 46, 62], anemia [63], hypertriglyceridemia [13], hypercalcemia [64], and high serum phosphate [60]. The other independent risk factor for sleep disorders was dialysis shift in the morning [49, 65].

Session 4 Summary of Literature Review

The literature review revealed that the QOS was highly related to the health of patients. The physician and researchers must to do not only improving survival rate and clinical outcome but also enhancing the quality of life and quality of sleep in ESRD patients. A better estimate of the prevalence of sleep disturbances in the generalized Taiwanese HD population is lacking because most of the reports about QOS studying in Taiwanese HD patients were localized in north Taiwan. To investigate the factors affecting the QOS in Taiwanese HD are important to in clinical and researchers.

Chapter 3 Research Methods

Session 1 Research Structure

The structure of this study was summarized in Figure 3-1. This study aims to explore that the relevant factors such as, demographic factors, co-morbidity factors, clinical factors, depression, and the RLS would influence the QOS in ESRD patients treated with HD in Taiwan.

Session 2 Study Hypothesis

To our knowledge, the major factors might be potentially influencing to quality of sleep in ESRD patients, such as, aging, gender, smoking, coffee intake, anemia, co-morbidity, depression, anxiety, stress, HD mode, and RLS. Our study hypothesis was building on the bases of literatures review above. To examine the distributions in patient's characteristic, co-morbidity, HD mode, clinical parameters, depression, RLS, and QOS in ESRD patients in Taiwan, we analyze the data that will be collected. Our hypotheses are as following:

1) Patients with severe depression symptom will have poorer QOS.
2) Patients with less RLS symptom will have better QOS.
3) There are some differences in patients' characteristic, co-morbidity, and HD mode between ESRD patients with poor and good QOS.

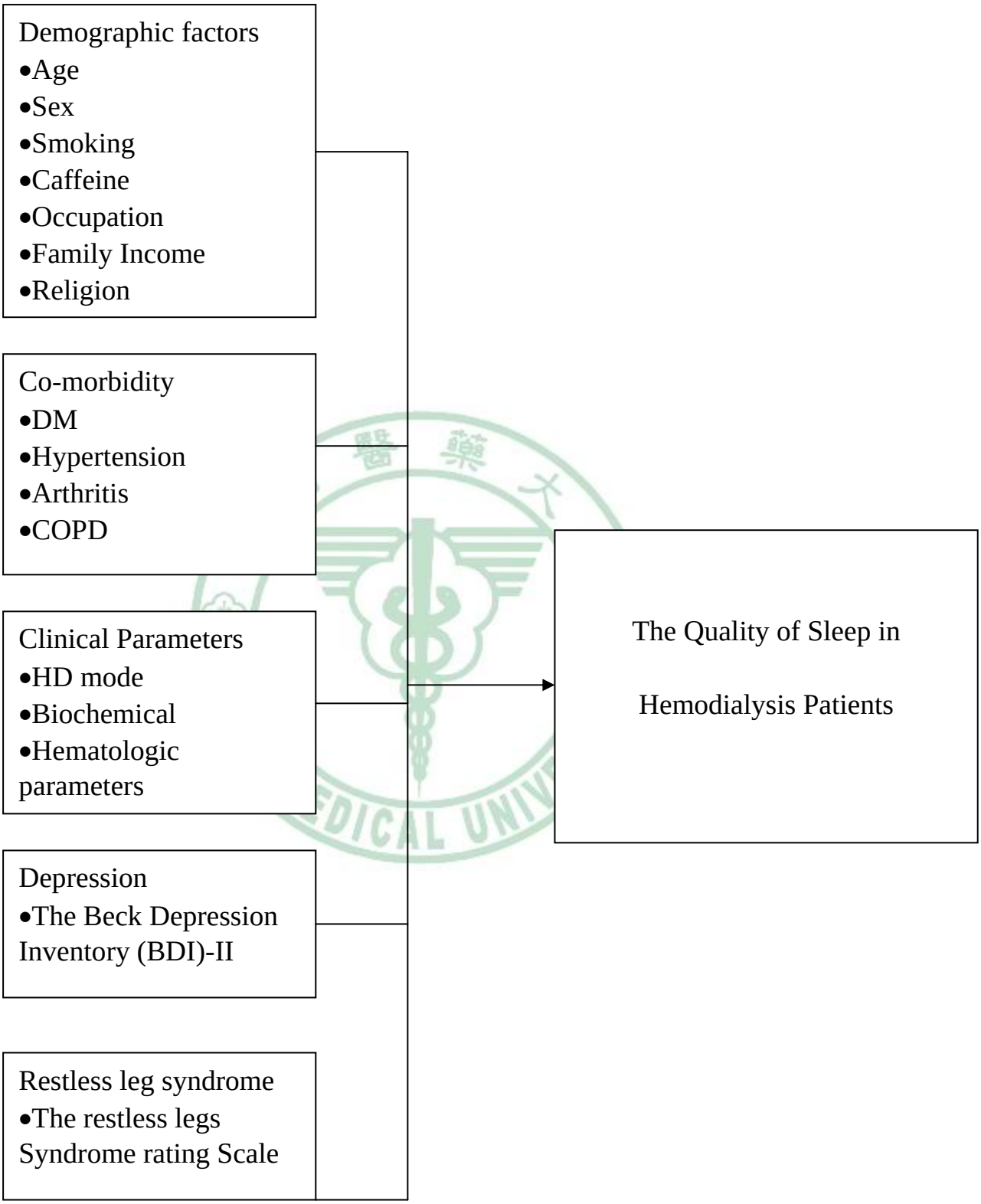

Figure 3-1 Research Structure

Session 3 Sample and Data Sources

The HD patients in Taiwan were the study population. The data used for the analysis were from sixty-three outpatients dialysis units located in Taiwan. The geographic representative samples of dialysis facilities were recruited after telephone communication. There were 17 facilities in Taipei Branch of Bureau of National Health Insurance (BNHI), 9 facilities in Northern Region Branch of BNHI, 20 facilities in Central Region Branch of BNHI, 8 facilities in Southern Region Branch of BNHI, and 9 facilities in Kao-Ping Branch of BNHI. Within each participating HD units, the patients were ranked from 1 to N before selected and one subject was randomly selected in number from one to ten by researcher without giving care, the next patient would be increase by ten, for example, ranked 5, 15, 25, and so forth. Patients with bed-ridden and poor communicated were excluded. The questionnaires were explained to each participant and informed consent was obtained (proved by the Ethical Committee of the Ching-Chyuan hospital, under monitoring by the Institutional Review Board). The patient's right to stop participating any time was reserved. If patient, such as, ranked five refused to join this study, patient ranked four then six replaced, and so on.

This cross-sectional study included data from 63 facilities (total facilities in Taiwan =449) with total random selected sample size of 374 patients (total patients number in Taiwan = 44,121). The average number in each participated facility was 6 patients. All patients had received HD for more than 3 months before enrolled in this study. The data regarding QOS, demographic factors, co-morbidity factors, HD mode, clinical parameters, depression, and the RLS were collected from Dec 2005 to Feb 2006. The Beck Depression Inventory-II (BDI-II, Chinese version), The International Restless Leg Syndrome rating scale (IRLS), and the Pittsburgh Sleep

Quality Index (PSQI) were collected using questionnaires translated to Chinese language and completed separately face-to-face by the HD unit nurse with training.

Session 4 Instruments

The PSQI is a standard self-administered questionnaire used to evaluate QOS [66]. This questionnaire has been widely used in measuring the QOS of dialysis and transplantation therapy in ESRD patients [15, 19, 67, 68] and chronic renal disease [69]. The questionnaire was previously translated into Chinese to assess the quality of sleep in Taiwan [13, 70] and Hong Kong [71]. The PSQI contains seven components with nineteen questions. The components are subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. Every component is scored from 0 to 3 and the total score yielded between 0 and 21, the lower scores displaying higher quality of sleep. The PSQI has been usefully separated ‘good sleeper’ and ‘poor sleeper’ in literature [13, 15, 66, 70, 71]. The cutting point of total scores greater than 5 indicates that a person is a ‘poor sleeper’.

The Beck Depression Inventory (BDI) is a self-rated questionnaire, has been used to assess patients for depression over forty-five years [72] and to investigate the depression symptom in ESRD patients [73]. The BDI-II was translated to Chinese by Chinese Behavioral Science Corporation and assesses the presence and severity of depression. It is a reliable and validated instrument of depression, existing high correlation with diagnostic criteria [74]. It has 21 items and scored from 0 to 3 then yielding global score of 0 to 63. A patient with BDI scores of 14 to19 indicates mild degree of depression, 20 to 28, a moderate degree, and 29 or greater, a severe degree of depression.

The International Restless Legs Syndrome rating scale (IRLS), ten-question scale measuring the severity of RLS, a patient-scaled tool has high levels of internal consistency and reliability [17, 75]. All the questions are rated in the range 0 to 4 (0=absence of a problem, 4=very severe problem), the global scores range between 0 and 40 (0=absence of a problem, 1 to 10=mild problem, 11 to 20=moderate problem, 21 to 30=severe problem, and 31 to 40=very severe problem). Test-retest reliability of the diagnosis was done in two weeks after data collected in 26 randomized patients from three facilities. The relationship between test and retest was determined based on Pearson's correlation coefficient. The Pearson's correlation coefficient of questionnaire was 0.78, showing the applicability of the scale.

Session 5 Measurement

The demographic data, clinical factors, HD mode, and laboratory parameters were recorded from the medical records. The operational definitions of variables in this study were listed in Table 3-1.

Table 3-1. Operational Definitions of Variables

Variable	Operation definition	Attribute
Demographics		
Age (years old)	From the birth day to December 2005	Ratio
Gender	Male, female. If female, before menopause (1), menopause (2)	Nominal
Education level	Nil, elementary school, junior high school, high school, junior collage, collage, master	Nominal
Marital status	Single, married, separated, widow/widower, divorced	Nominal
Occupation	None, part-time, day-time, night-time	Nominal
Family income (thousand)	(1)≦30, 30<(2)≦60, 60<(3)≦90, 90<(4)≦120, 120<(5)≦150, 150<(6)	Ordinal

Table 3-1. Operational definitions of variables (cont')

Variable	Operation definition	Attribute
Demographics		
Smoking	Yes, No	Nominal
Yes (pack)	(1)≦0.5, 0.5<(2)≦1, 1<(3)≦2, (4)>2	Ordinal
Caffeine	Yes, No	Nominal
Yes (cup)	(1)≦1, 1<(2)≦2, 2<(3)≦3, (4)>3	Ordinal
Religion	None, Taoism, Buddhism, Christian, Catholic, Muslim	Nominal
Hemodialysis and co-morbidity		
Causes of ESRD	Diabetes mellitus (DM), Hypertension (HT), Chronic glomerulonephritis (CGN), Systemic lupus erythematous (SLE), polycystic kidney disease (PKD)	Nominal
Co-morbidity	DM, HT, angina pectoris, heart failure (HF), myocardial infarction, cerebral vascular accident (CVA), chronic obstructive pulmonary disease (COPD), liver cirrhosis, chronic hepatitis, peripheral vascular disease, neoplasm, head injury, psychiatry disease	Nominal
Time on dialysis (years)	From the day of first time HD to December 2005	Ratio
Hemodialysis (HD) shift mode	HD in the Morning, afternoon, or at night	Nominal
HD times/per week	HD times per week, 1,2,3, >3	Ordinal
HD duration hours/per session	HD≦3, 3< HD≦3.5, 3.5< HD≦4, 4< HD	Ordinal
Clinical parameters and laboratory data		
Serum albumin (g/dl)	Pre-HD serum albumin value on December 2005	Ratio
Blood urea nitrogen (BUN) mg/dl	Pre-HD serum BUN value on December 2005	Ratio
Creatinine (Cr)	Pre-HD serum creatinine value on December 2005	Ratio
Urea reduction rate (%)	The percentage of (Pre-HD serum BUN minus Post-HD BUN)/ Pre-HD serum BUN	Ratio

Table 3-1. Operational definitions of variables (cont')

Variable	Operation definition	Attribute
Clinical parameters and laboratory data		
Kt/V (Daugirdas)	The Daugirdas method Kt/V = -ln(R-0.008*t) + (4-3.5* R) * UF/W, R=post-HD BUN/Pre-HD BUN, t = HD duration (hours), UF= ultrafiltration volume (Liter), W= Post-HD body weight (Kg), on December 2005	Ratio
Uric acid (mg/dl)	Pre-HD serum uric acid value on December 2005	Ratio
Total cholesterol (mg/dl) T-CHO	Pre-HD serum cholesterol value on December 2005	Ratio
Triglyceride (TG) (mg/dl)	Pre-HD serum triglyceride value on December 2005	Ratio
Na meq/L	Pre-HD serum sodium value on December 2005	Ratio
Ca * P	Pre-HD serum calcium value multiplier serum phosphate on December 2005	Ratio
Ferritin (ng/ml)	Pre-HD serum Ferritin value on December 2005	Ratio
K (meq/L)	Pre-HD serum potassium value on December 2005	Ratio
iPTH (pg/ml)	Pre-HD serum intact parathyroid hormone value on December 2005	Ratio
Iron (ug/dl)	Pre-HD serum iron value on December 2005	Ratio
Ca (mg/dl)	Pre-HD serum calcium value on December 2005	Ratio
GOT (IU/L)	Pre-HD serum GOT value on December 2005	Ratio
Total iron binding capacity (TIBC) (ug/dl)	Pre-HD serum TIBC value on December 2005	Ratio
P (mg/dl)	Pre-HD serum phosphate value on December 2005	Ratio
GPT (IU/L)	Pre-HD serum GPT value on December 2005	Ratio
Red Blood Cell ($*10^6$)	Pre-HD red blood cell on December 2005	Ratio
Hemoglobin (g/dl)	Pre-HD hemoglobin value on December 2005	Ratio
Hct (%)	Pre-HD Hct value on December 2005	Ratio

Table 3-1. Operational definitions of variables (cont')

Variable	Operation definition	Attribute
Clinical parameters and laboratory data		
Weight (Kg) before HD	The body weight of the patient before HD on December 2005	Ratio
Weight (Kg) after HD	The body weight of the patient after HD on December 2005	Ratio
Systolic BP (mmHg)	The systolic blood pressure before HD on December 2005	Ratio
Diastolic BP (mmHg)	The diastolic blood pressure before HD on December 2005	Ratio
Respiratory rate (time/minute)	The respiratory rate before HD on December 2005	Ratio
Heart rate (beats/minute)	The heart beats per minute before HD on December 2005	Ratio
Sedatives	The kinds of sedatives used by patient, nil, 1,2,3, >3	Ordinal
EPO (U/month)	The injection dose of erythropoitin per month	Ordinal
Ferritin supply	The injection dose of ferritin per month, nil, 100 mg, 400 mg, > 400mg	Ordinal
The Pittsburgh Sleep Quality Index (PSQI)		
Time to bed	When the patient has usually gone to bed	Ratio
Time to sleep (minute)	The time the patient need to fall asleep	Ratio
Time to get up	When the patient has usually gotten up in the morning	Ratio
Hours of sleep	Hours of actual sleep the patient got at night	Ratio
Trouble sleeping in the past month	How often has the patient had trouble sleeping, nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Cannot get to sleep within 30 minutes	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Wake up in the middle of the night or early morning	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal

Table 3-1. Operational definitions of variables (cont')

Variable	Operation definition	Attribute
Have to get up to use the bathroom	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
The Pittsburgh Sleep Quality Index (PSQI)		
Cannot breathe comfortably	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Cough or snore loudly	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Feel too cold	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Feel too hot	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Have bad dreams	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Have pain	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Taken medicine for sleep	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Trouble staying awake while engaging in social activity	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Problems for patient to keep up enthusiasm to get things done	Nil (0), less than once a week (1), once or twice a week (2), three or more times a week (3)	Ordinal
Patient rate his or her sleep quality overall	Very good (0), fairly good (1), fairly bad (2), very bad (3)	Ordinal
International Restless Legs Syndrome rating scale (IRLS)		
RLS discomfort in patient's legs or arms	(4) Very severe, (3) Severe, (2) Moderate, (1) Mild (0) None	Ordinal
RLS symptoms need to move	(4) Very severe, (3) Severe, (2) Moderate, (1) Mild (0) None	Ordinal

Table 3-1. Operational definitions of variables (cont')

Variable	Operation definition	Attribute
International Restless Legs Syndrome rating scale (IRLS)		
Relief from moving around	(4) Very severe, (3) Severe, (2) Moderate, (1) Mild (0) None	Ordinal
Sleep disturbance by RLS symptoms	(4) Very severe, (3) Severe, (2) Moderate, (1) Mild (0) None	Ordinal
Tiredness, sleepiness by RLS symptoms	(4) Very severe, (3) Severe, (2) Moderate, (1) Mild (0) None	Ordinal
Overall your RLS severity as a whole	(4) Very severe, (3) Severe, (2) Moderate, (1) Mild (0) None	Ordinal
RLS symptoms frequency	(4) Very severe (This means 6 to 7 days a week.), (3) Severe (This means 4 to 5 days a week.), (2) Moderate (This means 2 to 3 days a week.), (1) Mild (This means 1 day a week or less.), (0) None	Ordinal
RLS symptoms on an severe average day	(4) Very severe (This means 8 hours per 24 hour day or more.), (3) Severe (This means 3 to 8 hours per 24 hour day.), (2) Moderate (This means 1 to 3 hours per 24 hour day.), (1) Mild (This means less than 1 hour per 24 hour day.), (0) None	Ordinal
The impact of RLS symptoms on ability to carry out daily life	(4) Very severe, (3) Severe, (2) Moderate, (1) Mild (0) None	Ordinal
RLS symptoms on mood	(4) Very severe, (3) Severe, (2) Moderate, (1) Mild, (0) None	Ordinal
Beck Depression Inventory-II (BDI-II)		
Sad	(0) I do not feel sad.(1) I feel sad. (2) I am sad all the time and I can't snap out of it. (3) I am so sad or unhappy that I can't stand it.	Ordinal
Discouraged	(0) I am not particularly discouraged about the future. (1) I feel discouraged about the future. (2) I feel I have nothing to look forward to. (3) I feel that the future is hopeless and that things cannot improve.	Ordinal

Table 3-1. Operational definitions of variables (cont')

Variable	Operation definition	Attribute
Beck Depression Inventory-II (BDI-II)		
Failure experience	(0) I do not feel like a failure. (1) I feel I have failed more than the average person. (2)As I look back on my life, all I can see is a lot of failure. (3) I feel I am a complete failure as a person.	Ordinal
Dissatisfied	(0) I get as much satisfaction out of things as I used to. (1) I don't enjoy things the way I used to. (2) I don't get any real satisfaction out of anything anymore. (3) I am dissatisfied with everything the way I used to.	Ordinal
Guilty	(0) I don't feel particularly guilty. (1) I feel guilty a good part of the time. (2) I feel quite guilty most of the time. (3) I feel guilty all of the time.	Ordinal
Punished	(0) I don't feel I am being punished. (1) I feel I may be punished. (2) I expect to be punished. (3) I feel I m being punished.	Ordinal
Hate	(0) I don't feel disappointed in myself. (1) I am disappointed in myself. (2) I am disgusted with myself. (3) I hate myself	Ordinal
Blame	(0) I don't feel I am any worse than anybody else. (1) I am critical of myself for my weaknesses or mistakes. (2) I blame myself all the time for my faults. (3) I blame myself for everything bad that happens.	Ordinal
Suicide	(0) I don't have any thoughts of killing myself. (1) I have thoughts of killing myself, but I would not carry them out. (2) I would like to kill myself. (3) I would kill myself if I had the chance.	Ordinal
Cry	(0) I don't cry any more than usual. (1) I cry more now than I used to. (2) I cry all the time now. (3) I used to be able to cry, but now I can't cry even though I want to.	Ordinal

Table 3-1. Operational definitions of variables (cont')

Variable	Operation definition	Attribute
Beck Depression Inventory-II (BDI-II)		
Irritated	(0) I am no more irritated by things than I ever am. (1) I am slightly more irritated now than usual. (2) I am quite annoyed or irritated a good deal of the time. (3) I feel irritated all the time now.	Ordinal
Lost interest	(0) I have not lost interest in other people. (1) I am less interested in other people than I used to be. (2) I have lost most of my interest in other people. (3) I have lost all of my interest in other people.	Ordinal
Make decision	(0) I make decisions about as well as I ever could. (1) I put off making decisions more than I used to. (2) I have greater difficulty in making decisions than before. (3) I can't make decisions at all anymore.	Ordinal
Valueless	(0) I don't feel that I am valueless. (1) I am worried that I am more valueless than before. (2) I feel that am more valueless than another people. (3) I believe that I am completely valueless.	Ordinal
Lost energy	(0) I can work about as well as before. (1) It takes an extra effort to get started at doing something. (2) I have to push myself very hard to do anything. (3) I can't do any work at all.	Ordinal
Sleep habit change	(0) I can sleep as well as usual. (1a) I can sleep a little more as I used to. (1b) I can sleep a little less as I used to. (2a) I can sleep more as I used to. (2b) I can sleep less as I used to. (3a) I almost sleep all day long. (3b) I wake up s1-2 hours earlier than I used to and cannot get back to sleep.	Ordinal
Angry	(0) I don't get more angry than usual. (1) I get a little bit angry more easily than I used to. (2) I get angry more easily than I used to. (3) I get more angry anytime.	Ordinal

Table 3-1. Operational definitions of variables (cont')

Variable	Operation definition	Attribute
Beck Depression Inventory-II (BDI-II)		
Appetite	(0) My appetite is no change as before. (1a) My appetite is worse as usual. (1b) My appetite is better as usual. (2a) My appetite is much worse as usual. (2b) My appetite is much better as usual. (3a) I have no appetite at all. (3b) I want to eat foods anytime.	Ordinal
Concentrate on	(0) I can concentrate on anything as well as before. (1) I can concentrate as not well as before. (2) I cannot concentrate on anything for a long time. (3) I find that I cannot concentrate on anything.	Ordinal
Tired	(0) I don't get more tired than usual. (1) I get tired more easily than I used to. (2) I get tired from doing almost anything. (3) I am too tired to do anything.	Ordinal
Lost interested in sex	(0) I have not noticed any recent change in my interest in sex. (1) I am less interested in sex than I used to be. (2) I am much less interested in sex now. (3) I have lost interested in sex completely.	Ordinal

Session 6 Analytical Methods

The descriptive statistics was used for demographic variables, co-morbidity, HD mode, laboratory data values and blood parameters in this study. The percentage, mean and standard deviation (SD) were used to describe the operational definition of variables. The categorical variables compared between the 'good sleeper' and 'poorer sleeper' were analyzed by the chi-square test or the Fisher exact test, as appropriate. Continuous variables were analyzed with student's t-test. We used multiple linear regression analysis to investigate the significant factors affecting the global PSQI scores. Independent variables entered into the models including all variables that were significantly different in bivariate analysis, or clinical relevant

reviewed from literature. We used stepwise methods to build the multiple regression models. A two-tailed P value < 0.05 was considered statistical significance. A standard statistical package SAS software (version 8.01) was used to perform all calculations in this study.

Chapter 4 Results

Session 1 Descriptive Analyses

- Demographic

The demographic characteristics of subjects are shown in Table 4-1 and Table 4-2. There were 348 patients in the final study sample. The response rate was 93.05%. Mean age of population was 60.47 ± 13.92 years (range, 20.17 to 92.33). The proportion of female was 52.3%. Sixty-six patients had never gone to school. The education levels, 124 patients (35.63%) graduated from elementary school, 57 patients (16.38%) graduated from junior high school, 64 patients (18.39%) graduated from high school, and 37 patients (10.64%) graduated from collage or above.

The marital status, they were 264 married (76.3%), 36 widow or widower (10.4%), and 14 separated or divorced (4.1%). The proportion of occupational status of subjects without work was 78.9 %, with part-time work was 8.5%, with full daytime work was 11.7%, and with full nighttime work was 0.9%. The family income (NT$ thousand) were less than or equal to 30 (37.46%), between 30 to 60 or equal to 60 (40.25%), between 60 to 90 or equal to 90 (12.07%), between 90 to 120 or equal to 120 (6.5%), and greater to 120 (3.72%). In personal habits, 14.8% of cases were smokers, and 14% of patients had caffeine consumption lifestyle. Similar to Taiwanese religion distribution, most of patients were Buddhist and Taoist (76.3%), none of religion (19.6%), Christian and Catholic (3.5%), and others (0.6%).

- Etiology of ESRD and Co-morbidity

The most prevalent end stage renal disease was chronic glomerulonephritis

(41.95%). The other causes of ESRD were DM (33.6%), hypertension (9.77%), PKD (2.01%), and SLE (1.44%). Other or unknown etiology of ESRD accounted for 11.2% of patients. The co-morbidity was distributed as HT (35.9%), DM (17.9%), chronic hepatitis (10.8%), and HF (4.6%). The proportion of sum of co-morbidity number as following: none was 33.5 %, one was 46 %, two was 16.38 %, and ≧ 3 was 4.6 %..

- Clinical Parameters

The ESRD patients have been treated on maintenance dialysis for a mean of 4.68 ± 4.27 years (range, 0.2 to 22 years). Forty-four percent of the patients dialyzed in the morning, 42.4% of the patients dialyzed in the afternoon, and 13.8 % of the patients dialyzed at night. Most of HD patients (96.3%) dialyzed 3 times per week. Only 3.7% dialyzed two or four times per week. Most of the each HD session was between 3.5 to 4 hours (73.5%). There were 19% of patients received each HD session greater than 4 hours. The average Pre-HD/Post-HD weight of subjects was 61.1/58.36 Kg. The average ultrafiltration rate per HD session was 2.78 Kg. The average blood pressure (SBP/DBP) before HD was 138.63/77.61 mmHg. The heart rate was between 59 and 102 beats per minute. The respiratory rate ranged from 12 to 22 times per minute.

- Biochemical and Hematologic Parameters

The serum albumin level varied from 2.4 g/dl to 5.3 g/dl with mean of 3.9 (±0.4) g/dl. Pre-HD BUN ranged from 34 mg/dl to 134.7 mg/dl with mean of 73.47 (±19.05) mg/dl. Mean and SD of urea reduction rate was 71.19 ± 6.83% and the range from 35% to 95%. The Kt/V (Daugirdas) ranged from 0.73 to 2.04 with average of 1.48. The mean of pre-HD creatinine level was 10.86 ± 2.79 mg/dl (range from 3.8 to 24.1) mg/dl. The serum uric acid had a range of 3-12.4 mg/dl with average of 7.39 mg/dl. Total cholesterol varied from 65 mg/dl to 526 mg/dl

with average of 177.73 ± 46.93 mg/dl. Triglyceride was between 32 mg/dl and 1040 mg/dl with mean of 161.37 ± 123.04 mg/dl.

The serum sodium measured from 128 meq/L to 147 meq/L with mean of 138.29 ± 3.47 meq/L. The serum potassium varied from 2.8 meq/L to 7.2 meq/L and mean of 4.71 ± 0.78 meq/L. The mean of total serum calcium was 9.54 ± 0.86 mg/dl and range from 12.8 mg/dl to 6.8 mg/dl. The serum phosphate checked from 1.4 to 12.4 mg/dl and the mean was 5.1 ± 1.62 mg/dl. The calcium phosphate product was between 11.9 and 109.1 with mean of 49.07 ± 16.14. The intact parathyroid hormone varied from 0.5 pg/ml to 1687.7 pg/dl and average of 235.86 ± 290.98 pg/dl. The GOT value was 6 IU/L to 242 IU/L with mean of 24.92 ± 21.17 IU/L. The GPT leveled from 2.4 IU/L to 154 IU/L with mean of 23.61±20.43 IU/L.

The serum ferritin ranged from 3.8 ng/ml to 6755ng/ml with mean of 596.8 ± 615.06 ng/ml. The serum iron varied from 2 ug/dl to 239 ug/dl with mean of 78.22 ± 39.35 ug/dl. The TIBC was between 44.1 ug/dl and 432 ug/dl and average of 224.28 ± 49.07 ug/dl. The red blood cells observed 1.99 million per milliliter to 9.2 million per microliter with mean of 3.46±0.8 million per microliter. The hemoglobin measured was 6.4 g/dl to 15.7 g/dl with mean of 10.51 ± 1.4 g/dl. The white blood cells ranged from 2.6 to 20.8 thousand per milliliter and average of 6.54 ± 2.21 thousand per milliliter. The hematocrit checked between 19% and 47% with mean of 31.48 ± 4.06%.

There were 48.7 % of patients that had used sleep medications. The percentage of patients used two or more sleep medications were 4.5%. Only three patients had never received the erythropoitin (EPO). The dosage of EPO used for patients and the percentage of patients were less than 10000 (25.95%), 10000 to 18000 (32.65), 18000 to 26000 (26.53%), and greater than 26000 (14%) units per month. There were 17.7% of patients that had received 100 mg ferrous injection per month. Six

percent of patients had received 400 mg ferrous injection per month. Only 3.18% of patients had received more than 400 mg iron supply per month.

- Quality of Sleep

The PSQI global score of study patients had a range of 0-21 points with mean of 8.49 ± 4.64 points. For the individual components, each observed ranges were 0-3 points. The subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction had mean of 1.34 ± 0.88, 1.79 ± 0.98, 1.03 ± 1.08, 1.03 ± 1.21, 1.36 ± 0.63, 1.14 ± 1.34, and 0.79 ± 0.80.

- RLS and Depression

The restless legs syndrome rating scale revealed a range of 0 to 40 points with mean and SD of 14.25 ± 11.48 in HD patients. There were 26.93 % of the ESRD patients on mild severity of RLS symptom. Nine percent of the ESRD patients had moderate symptom of RLS. On severe and very severe symptom, there were 8.05% and 7.43% of the ESRD patients. The total Beck depression inventory (BDI-II) score of 0-13 were 57.47% of the ESRD patients. The mean and SD of the BDI-II scores were 7.05 ± 8.62. There were 14.94 % of subjects with score of 14-19 points in the BDI-II that were considered mild depression. Sixteen percent of cases had BDI-II score of 20-28 points that were regarded as moderate depression, 12.07% of patients greater than 28 points as severe depression.

Session 2 Bivariate Analyses

The cases of this study were divided into two groups by QOS, the global PSQI > 5 as the ‘poor sleepers’ including 223 patients (66%) and global PSQI≦5 as the ‘good sleepers’ including 115 patients (34%). The comparisons of variables between ‘poor sleepers’ and ‘good sleepers’ were represented in Table 4-3.

There was no significant difference in age distribution between ‘poor sleepers’ and ‘good sleepers’ ($p>0.05$). Compared with ‘good sleepers’, ‘poor sleepers’ had a greater proportion of female ($p<0.05$). In addition, it was significant difference by proportion of graduate from junior high school or above in ‘good sleepers’ (51.3%) compared with ‘poor sleepers’ (42.48%) ($p<0.05$). Also, the higher proportion (81.66%) of patients without work was found in ‘poor sleepers’, and the proportion of none occupational status in ‘good sleepers’ was 73.21% ($p<0.05$). Conversely, no significant differences existed to compare two groups in the religious belief ($p>0.05$). The marital status was similar in ‘poor sleepers’ and ‘good sleepers’ ($p>0.05$). The proportion of lower family income was higher in ‘poor sleepers’ compared with ‘good sleepers’, but these trends did not reach statistical significance ($p>0.05$).

In HD-related factors, there was no significant difference in time on dialysis between ‘poor sleepers’ and ‘good sleepers’ ($p>0.05$). It was similar in frequency on dialysis between two groups ($p>0.05$). The duration of per HD session was also similar between ‘poor sleepers’ and ‘good sleepers’ ($p>0.05$). Mean ultrafiltration of ‘poor sleepers’ was still similar to mean ultrafiltration of ‘good sleepers’ ($p>0.05$). Especially, it reached significantly differences to compare ‘poor sleepers’ with ‘good sleepers’ in HD shift mode ($p<0.05$).

The ratio of using of sleep medicine was higher in ‘poor sleepers’ (61.68%)

compared with ‘good sleepers’ (21.3%) ($p<0.05$). Contrarily, there was no significant difference in dosage of EPO ($p>0.05$) and ferrous supply ($p>0.05$) per month between two groups. In personal habits, there was also no significant difference in smoking ($p>0.05$) and coffee consumption ($p>0.05$) between ‘poor sleepers’ and ‘good sleepers’.

In clinical variables, there were no significant differences between ‘poor sleepers’ and ‘good sleepers’, including serum albumin, BUN, serum creatinine, uric acid, total cholesterol, TG, GOT, GPT, sodium, potassium, and phosphate. Only mean serum calcium was higher in ‘poor sleepers’ compared with ‘good sleepers’, but these were not statistically significant difference ($p>0.05$). The mean intact parathyroid hormone was also higher in ‘good sleepers’ compared with ‘poor sleepers’, but the difference approached statistical significance ($p>0.05$). In hematologic factors, there were no significant differences in RBC ($p>0.05$), hemoglobin ($p>0.05$), and hematocrit ($p>0.05$) in ‘poor sleepers’ compared with ‘good sleepers’. Most of the physical factors were similar between ‘poor sleepers’ and ‘good sleepers’. Specifically, the pre-HD weight ($p>0.05$) and post-HD weight ($p>0.05$) were similar between the groups ‘poor sleepers’ and ‘good sleepers’. There were no statistically significance systolic BP ($p>0.05$), diastolic BP ($p>0.05$), heart rate ($p>0.05$), and respiratory rate ($p>0.05$) in ‘good sleepers’ compared with ‘poor sleepers’.

The occurrence of RLS symptoms influenced the sleep status, the higher RLS rating score was found in ‘poor sleepers’ compared with ‘good sleepers’ ($p<0.05$). The depression symptoms were evidently related to sleep quality. The proportion of moderate and severe in BDI-II scale was higher in ‘poor sleepers’ (34.33%) compared with ‘good sleepers’ (15.92%). It was significant differences to compare ‘poor sleepers’ and ‘good sleepers’ in BDI-II score ($p<0.05$)

Session 3 Multiple Linear Regression

We used multiple linear regression to predict a score of global PSQI in HD patients based on the independent variables. The percentage of the variation of global PSQI explained by all the independent variables after adjusting in this model is 36% (Adj $R^2 = 0.36$). Multiple linear regression model with PSQI score on HD patients was listed in Table 4-4.

Table 4-4 showed the estimated parameters of multiple linear regression model for the variables of the HD patients. In this model, the independent effect of each variable could be seen after controlling for the other variables. The significant variables were age, family income, sleep medicine, IRLS, and BDI-II.

After adjusted, patients with every additional year will increase 0.04 points in the global PSQI ($p<0.05$). The patients with family income > 60 thousands per month are predicted to have 1.14 points decrease in global PSQI than those with family income ≦ 60 thousands ($p<0.05$). The patients taking sleep medicine associated with 3.83 points higher in global PSQI than patients without sleep medicine ($p<0.05$). Patients with one more point IRLS will increase 0.1 points in the global PSQI ($p<0.05$).

After controlling for the effects of other variables, the predicted global PSQI for patients with BDI-II score 14-19, 20-28, and >28 are 1.68, 2.13, and 2.54 points higher than those with BDI-II score 0-13 ($p<0.05$). The more severe degree of BDI-II score is more positive significantly correlated with global PSQI score.

After taking the other variables into account, the predicted global PSQI was not significant for gender, time on dialysis, HD shift mode, number of co-morbidity, education status, marital status, occupation status, smoking, and coffee drinking ($p>0.05$).

Chapter 5 Discussion

In this study sample, the mean age of population was 60.47 ± 13.92 years, similar to 60.11 ± 13.69 years in Taiwanese HD population in 2005 [5]. The proportion of female was 52.3% of patients, rather close to the proportion of female in HD patients in Taiwan [20]. After analyzed the age and gender distribution of sample with good of fit test, there was no significant difference.

Our study skips off the weakness of previous surveys on sleep disturbances in ESRD patients on maintenance HD in Taiwan. The patients assessed in this study are widely distributed in Taiwan and do not limit to centers in homogenous geographic district. The second shortcoming that we overcame is the sample size and patients were selected by systematic random selection in this study. Another weak point bypassed is the dialytic strategy by physicians setting, whereas patients were dialyzed in 63 different facilities. These facilities distributed from hospital-based to clinic-based units. This permits us to exclude the deviation of therapeutic policy by single center or multiple centers with similar physician training program from same health care system. Furthermore, the previous studies in Chinese ESRD patients with sleep disturbances have focused on CAPD or description of small sample size in HD without or with intervention [13, 19, 55, 77, 78]. Thus, we divided the HD patients into two groups and compared them, avoided the different therapeutic bias between groups.

After first report of sleep disorders in HD patients by Strub et al. [37] in 1982, our study still clearly presents high prevalence of sleep complaints in HD patients. Our data revealed that age, family income, sleep medicine, RLS symptom, and depression are significantly independent variables related to QOS. Whereas gender, time on dialysis, sum of number of co-morbidity, education status, occupation status,

lifestyle behavior, and marital status are not the significant determinant of QOS.

The mean global PSQI scores was 8.49 ± 4.64, similar to 8.7 ± 4.5 in Canadian HD population reported by Iliescu et al. [15]. Compared with scores of normal healthy control group from Buysse et al. [66], 2.67 ± 1.7, the global PSQI scores revealed rather poor quality of sleep (QOS) in our HD patients. Another study [76] in elder Taiwanese with mean age of 70.22 years, the global PSQI scores was 6.13 ±1.1. The scores were still lower than our HD patients. The prevalence of sleep complaints in this study was 66%. Whereas Hui et al. [13] reported that the prevalence of sleep complaints in CAPD patients was 52% in Taiwan, but they definite the 'poor sleepers' when global PSQI scores over 8. The similar result that 61% of patients had self-reported sleep disorders was reported in Hong Kong [55]. This study is also similar to the 50-86% prevalence of sleep-wake complaints in Caucasian HD populations expressed in previous studies [12, 14, 15, 46, 49, 78]. The mean score for seven components of the PSQI in our HD patients, Canadian HD population [15], US healthy control [66], and elder Taiwanese [76] are shown in Figure 5-1. Figure 5-2 shows the mean score in the seven components of all HD subjects, 'poor sleepers', and 'good sleepers' in this study. The mean score in the seven components revealed the highest score in sleep latency. It meant that HD patients were difficult to initiate a falling asleep, similar to previous studies [15, 76]. The best performance in the seven components of sleep quality was daytime dysfunction. The mean scores of daytime dysfunction were lower in our HD patients than Canadian HD population (0.79 *vs* 1.08) [15] and elder Taiwanese (0.79 *vs* 1.08) [76]. The differences of daytime dysfunction between HD patients and elder Taiwanese might be due to the age. Another reason, the proportion of patients without work might be the contributing factor. The daily activity of patients is free from work and keeping up enough enthusiasm to get thing done is not so important

to patients. The differences of daytime dysfunction between Taiwanese and Canadian HD patients need to further study.

Both quality and efficiency of sleep were significantly worse in ‘poor sleeper’ than ‘good sleeper’. It was reasonable that there was significantly higher proportion of using sleep medicine in ‘poor sleeper’ than ‘good sleeper’. Contrarily, the proportion of using sleep medicine in ‘good sleeper’ was also 21.3%. In other words, the higher prevalence of HD patients with sleep disturbances may be found. An important and urgency message to health care system of the differences in QOS is the advanced evidence of a 48.66% prevalence of using sleep medicine in this HD population.

The age was significantly related to QOS in this study. Despite this study was similar to previous studies [14, 49, 59], it was different to the study of Chinese CAPD patients in Hong Kong [55] and study of US [12]. One of the most common complaints of elder is difficult to fall asleep. This problem results in daytime napping and poor sleep efficiency, poor concentration and memory, even increasing risk of accident. Aging is a nature process with change in the circadian rhythms. The decreased level with age in neurohormone melatonin had been found to play an important role in the circadian rhythms and quality of sleep in human survey [80] and dove study-the animal with similar circadian rhythms to human [81]. However, a study found that the mean melatonin concentrations of HD patients were significantly higher compared with that of intact kidney controls [82]. Hence, the true reason of changing sleep quality of HD patients with aging is still unclear. Furthermore, in our study, ‘poor sleepers’ had a greater proportion of female, but there was no significant relationship after adjusting the difference of the other variables. Contrarily, poor QOS was significantly related to male gender reported by another studies [14, 60]. Kimmel et al. [83] surveyed 26 HD patients with sleep

disturbances by polysomnography and found that there was no difference in gender.

High TG was found to associate with global PSQI by study in Taiwanese CAPD patients [13]. The other factor, phosphate, had also been reported that it was related with QOS [60]. There was also no significant difference of metabolic data between 'good sleepers' and 'poor sleepers' in our study. The urea reduction rate and Kt/V (the measurements of small solute clearance), both were not significant difference between 'poor sleepers' and 'good sleepers'. Hanly et al. [62] found that sleep latency in 58% of 24 HD patients was associated with BUN, but the others [12, 14, 15, 54] reported that there was no relationship between sleep latency and BUN. A study reported that the Kt/V was not correlated to sleep behaviors [54]. There was also no relationship between Kt/V and sleep quality in Canadian HD patients [15]. Hanly and Pierratos found that the improvement of sleep apnea was significantly in patients with lower creatinine undergoing nocturnal HD than conventional HD [43]. A study with objective polysomnography measures of nocturnal sleep in the CKD patients and HD patients with the similar metabolic data in 2005 [48], the authors suggested that the differences of sleep disturbances in the chronic renal disease patients and HD patients may be due to different etiologies. It may not be possible to find the effect on sleep quality by the laboratory parameters going. Another word, we need a more delicate measurement to detect the difference (such as on line day-to-day measurements of solute removal) or measurements of another solute removal that is still unused. Another measurement to check a substance with larger molecular weight (like the β_2-microglobulin) is necessary for the evaluation of HD adequacy.

The socio-economic, psychological factors, and intrinsic sleep disruption (RLS, PLMS) may play a more important role in HD patients. It is well known that uremia and dialysis have medical, social, and economical consequences, both for the

individual with dialysis and for Bureau of National Health Insurance (BNHI). The proportion of the patients without occupation status in this HD population run up to 78%, three persons of 4 people are out of work. The lost of productivity makes patient sad, worry, even depression due to illness. The morbidity cost was inevitably high due to absence from work. Most of the family with a member of ESRD patient suffered from financial tension. The economic burden bothered the patient, and the poor quality of sleep was the result. A study on Canada general population revealed low family income was correlated to sleeping difficulties [84]. Our study also found that the HD patients with family income less than NT $ 60,000 per month in Taiwan was significantly inverse correlation to the quality of sleep. This result agrees with previous survey from the cohort study of general population with middle-aged in US [85]. That study found that annual family income below 50,000 dollars and depressive symptoms were predictors of insomnia complaints [85].

Although the incidence of restless legs symptom in our HD patients is 51.4%, it was much higher than that reported from other countries [56, 18, 79]. It was similar to that reported by Walker et al. (57.4%) [14], but it was still lower than that of HD patients in Hong Kong (70%) [78] and HD patients in US (83%) [12]. In spite of different estimation in prevalence of RLS was persistent in previous studies, it might be due to different race, culture, socio-economic supports, and therapeutic styles. The most important reason is that the diagnosis of restless legs by different criteria described. RLS represents a complex phenomenon that is difficult to measure objectively. However, the exact results may vary between individuals with ambiguously definite criteria. Furthermore, applying a uniform tool to investigate in RLS field is a good method. A convenient instrument to widely survey and easily compare with other studies is the consent. The IRLS is suitable to play the role for widely surveying in HD patients [75].

Our finding's clinical implication of restless legs symptom is reflected on quality of sleep. This study revealed that the proportion of severe restless legs symptom by IRLS was 15.48 % of HD patients, similar to report of Unruh et al. [18]. They also found that the sleep-quality score was significantly lower in dialysis patients with severe restless legs symptom after adjusting for other factors. In addition, they reported that the worse health related quality of life and shorter survival time were found in dialysis patients with severe restless legs symptom. In US, a study presented the significantly decreased survival time in patients with RLS by polysomnography after taking age, gender, and time on dialysis into account [39]. The Framingham Heart Study [44] found right ventricular wall thickness was associated with sleep-disordered breath. In Italy, a study reported that sleep apnea inducing hypoxemia was associated with cardiovascular events [45]. All of these three studies found that the patients complained the fragmented sleep at night. More severe RLS that the patients complained more urge to move at night resulted the fragmented sleep. Poor QOS are the sequence of severe RLS.

Many studies reported that ESRD patients had psychologic problems, such as depression, sadness, anxiety, worry, and stress [12, 54, 56, 69, 73]. We found highly significant correlation between the PSQI scores and BDI scores. This was also similar to the previous study that reported the association between quality of sleep and depression in ESRD patients in Canada [15]. In our experience, the prevalence of depression in HD patients was higher than general population, which is one of the most common psychiatric problems in HD population. In this study, there were over 40 % of patients with mild to severe degree of depression symptom. Most of the depressive patients have never been referred to psychiatrist. Depression is one of diseases in HD patients that is easily underdiagnosed and ignored by health care system [86, 87]. In 2006, a study reported that the prevalence of depression in HD

patients was 38.7% and 41.9% measured by BDI-II ≧14 and nurses' diagnosis in Canada [87]. A cross-sectional study in 12 countries with 9382 HD patients by random selection revealed that the prevalence of depression by Center for Epidemiological Studies Depression Sceening Index (CES-D) was 43 %, but only 2 % (Japan) to 21.7 % (United State) was diagnosed by physician [87]. There are a lot of patients with depression without adequate exploration. A convenient and valid instrument is needed to screen depression widely in HD patients. We also found that the levels of severity in depression were positively significant association with the poor quality of sleep. The psychosocial factors are highly associated with survival rate and hospitalization, especially depression [87]. Same as general population, HD patients have high suicide rate [88]. Early diagnosis of depression can help ESRD patients who are at higher risk of suicide. Psychologic interventions can release partial burden on patients, which can prevent the tragedy. In US, a study reported that higher levels of perceived social support were significantly inverse relationship to mortality risk [89]. They also reported that quantifying depressive symptom by BDI was a risk factor to survival.

Our study was multi-facility with large systematic random selected samples. The age and gender distribution is similar to national HD population [5, 20]. It may be possible to generalize to Taiwanese HD patients after increasing the sample size and conducting a long-term cohort study.

Chapter 6 Conclusion and Recommendations

This multiple-facility study found that the prevalent rate of sleep complaints in ESRD patients treated with maintain HD in Taiwan was 66%. Age, less family income, usage of sleep medicine, RLS symptom, and depression are independently associated with poorer quality of sleep in ESRD patients treated with HD.

Our study recommends that:

1. Apart from clinical therapy, our healthcare system may try to offer a convenient, reliable, and valid tool to survey RLS in HD patients.

   It will help clinical HD teams to find out the RLS in HD patient earlier and refer patients to neurologist for diagnosis and treatment.
2. Further psychologic supports from family or psychotherapeutic treatment will be necessary for HD patients with depression to improve the quality of sleep.

   It is useful to find out the depressive patients and refer patients to psychologist as early as possible.
3. More studies with cohort investigation on RLS and quality of sleep in ESRD patients are imperative.

   This study is cross-sectional survey and many limitations about causal relation would be inevitable. More comprehensive survey and more cohort explorations are the vital elements to make clear between RLS and quality of sleep, even the quality of life.

Chapter 7 Research Limitations

This analysis study was based on the subject-reported about depression, RLS, and QOS. Noted limitations included objective measurement of depression, RLS, and QOS. It is necessary to evaluate the depression by psychiatric criteria after screening and to survey the other psychological factors, such as anxiety, worry, and stress. Also, the other limitation is that this study doesn't include the medical center. Some bias will be eliminated after medical center included. A cohort study with sleep architectural integrity design is needed for completely drawing causally relational conclusion. The factors affecting sleep problems in ESRD on maintenance HD in Taiwan still remain to be elucidated in the future.

Table 2-1. Manifestations of the Uremic Syndrome

Neurologic
Central
Daytime drowsiness and a tendency to sleep progressing to increasing obtundation and eventual coma
Decreased attentiveness and cognitive tasking
Imprecise memory
Slurred speech
Asterixis and myoclonus
Seizures
Disorientation and confusion
Peripheral
Sensorimotor peripheral neuropathy, often with burning dysesthesia
Singultus
Restless leg syndrome
Increased muscle fatigability and muscle cramps
Cardiovascular
Accelerated atherosclerosis
Cardiomyopathy
Pericarditis
Pulmonary
Atypical pulmonary edema
Pneumonitis
Fibrinous pleuritis
Gastro-intestinal
Anorexia progressing to nausea and vomiting
Stomatitis and gingivitis
Parotitis
Peptic ulcer diathesis
Gastritis and duodenitis
Enterocolitis
Pancreatitis
Ascites

Table 2-1. Manifestations of the Uremic Syndrome (cont')

Dermatologic
Pruritus
Dystrophic calcification
Changes in skin pigmentation
Hematologic
Anemia
Altered neutrophilic chemotaxis
Depressed lymphocyte function
Bleeding diathesis with platelet dysfunction
Endocrinologic
Secondary hyperparathyroidism
Carbohydrate intolerance due to insulin resistance
Type IV hyperlipidemia
Altered peripheral thyroxine metabolism
Testicular atrophy
Ovarian dysfunction with amenorrhea, dysmenorrheal, dysfunctional uterine bleeding, cystic ovarian disease
Ophthalmic
Conjunctival or corneal calcifications

Source: May RC, Mitch WE: pathophysiology of uremia. In: Brenner and Rector's the kidney/edited by Barry M. Brenner, 5th ed. pp 2149.

Table 2-2. Potentially Toxic Compounds That Accumulate in Renal Failure

Urea	Pyridine derivatives
Phenols	Guanidine compounds
Indoles	β 2-Microglobulin
Skatoles	Aliphatic amines
Hormones	Hippurate esters
Polyamines	Middle molecules
Trace elements	Aromatic amines
Serum proteineases	

Source: May RC, Mitch WE: pathophysiology of uremia. In: Brenner and Rector's the kidney/edited by Barry M. Brenner, 5th ed. pp 2150.

Table 2-3. The Karnofsky score in ESRD Patients in Taiwan.

Karnofsky score	Patient (%)	Patient's status
100	17.7	Normal, no complaints or evidence of disease.
90	27.2	Able to perform normal activity; minor signs and symptoms of disease.
80	13.6	Able to perform normal activity with effort; some signs and symptoms of disease.
70	15.6	Care for self, unable to perform normal activity or do active work.
60	12	Requires occasional assistance but is able to care for most of own needs.
50	10.3	Requires considerable assistance and frequent medical care.
40	2.9	Requires special care and assistance; disabled.
30	0.2	Hospitalization indicated, although death not imminent; severely disabled.
20	0.3	Hospitalization necessary; active supportive treatment required, very sick.
10	0.1	Fatal processes progressing rapidly; moribund.

Source: Yang WC, Hwang SJ, Chen YM, Taiwan Society of Nephrology. Taiwan renal registry of end-stage renal disease patients and establishment of clinical performance measures. Acta Nephrologica 2004; 18(1):S1-S52

Table 4-1. Characteristics of the Subjects

Variable	N	Mean	(SD)	Max	Min
Demographic Characteristics					
Age	336	60.47	13.92	92.33	20.17
Haemodialysis Model					
Time on dialysis (Years)	346	4.68	4.27	22.00	0.2
Clinical Variables					
Biochemical and Electrolytes					
Serum albumin (g/dl)	342	3.90	0.40	5.30	2.40
BUN(Pre-HD)(mg/dl)	348	73.47	19.05	134.70	34.00
Cr. (Pre-HD)(mg/dl)	347	10.86	2.79	24.10	3.80
Uric acid (mg/dl)	343	7.39	1.59	12.40	3.00
URR (%)	344	71.19	6.83	95.00	35.00
Kt/V (Daugirdas)	344	1.48	0.25	2.04	0.73
T-CHO (mg/dl)	341	177.73	46.93	526.00	65.00
TG (mg/dl)	342	161.37	123.04	1040.00	32.00
Na (meq/L)	341	138.29	3.47	147.00	128.00
K (meq/L)	348	4.71	0.78	7.20	2.80
Ca (mg/dl)	348	9.54	0.86	12.80	6.80
P (mg/dl)	348	5.10	1.62	12.40	1.40
Ca*P	335	49.07	16.14	109.10	11.90
iPTH	342	235.86	290.98	1687.70	0.50
GOT (IU/L)	341	24.92	21.17	242.00	6.00
GPT (IU/L)	348	23.61	20.43	154.00	2.40
Ferritin (ng/ml)	347	596.80	615.06	6755.00	3.80
Iron (ug/dl)	335	78.22	39.35	239.00	2.00
TIBC (ug/dl)	343	224.28	49.07	432.00	44.10
Iron/TIBC (%)	340	38.10	0.27	271.88	2.51
Hematology					
RBC*106	339	3.46	0.80	9.20	1.99
Hb (g/dl)	348	10.51	1.40	15.70	6.40
Hct(%)	347	31.48	4.06	47.00	19.00

Table 4-1. Characteristics of the Subjects (cont')

Variable	N	Mean	(SD)	Max	Min
Physical					
Weight (Pre-HD)	343	61.10	11.53	124.70	35.40
Weight (Post-HD)	343	58.36	11.07	117.40	32.50
Ultrafiltration	334	2.78	1.09	7.30	0.10
Systolic BP (mmHg)	341	138.63	21.81	201.00	70.00
Diastolic BP (mmHg)	338	77.61	9.71	100.00	40.00
Respiratory rate	327	17.95	1.98	22.00	12.00
Heart rate	344	76.70	6.58	102.00	59.00
Quality of sleep					
Global PSQI	348	8.49	4.64	21	0
Subjective sleep quality	348	1.34	0.88	3	0
Sleep latency	348	1.79	0.98	3	0
Sleep duration	345	1.03	1.08	3	0
Sleep efficiency	348	1.03	1.21	3	0
Sleep disturbance	348	1.36	0.63	3	0
Use of sleep medications	348	1.14	1.34	3	0
Daytime dysfunction	348	0.79	0.80	3	0

PSQI, Pittsburgh Sleep Quality Index.

Table 4-2. Characteristics of the HD subjects

Variable	N	%
Demographic Characteristics		
Gender		
Male	166	47.70
Female	182	52.30
Education status		
Illiterate	66	18.97
Elementary school	124	35.63
Junior high school	57	16.38
Senior high school	64	18.39
College or above	37	10.64
Marital status		
Single	32	9.25
Married	264	76.30
Separated	4	1.16
Widowed	36	10.40
Divorced	10	2.89
Occupation status		
None	269	78.89
Part-time	29	8.50
Full day-time	40	11.73
Full night-time	3	0.88
Family Income NT $ (FI) (Thousand)		
FI≦30	121	37.46
30＜FI≦60	130	40.25
60＜FI≦90	39	12.07
90＜FI≦120	21	6.50
FI＞120	12	3.72
Smoke		
Yes	51	14.83
No	293	85.17

Table 4-2. Characteristics of the HD subjects (cont')

Variable	N	%
Demographic Characteristics		
Coffee		
Yes	48	13.99
No	295	86.01
Religion		
None	66	19.58
Taoism/ Buddhism	257	76.26
Christian/ Catholic	12	3.56
Other	2	0.59
Etiology of ESRD		
CGN	146	41.95
DM	117	33.6
Hypertension	34	9.77
PKD	7	2.01
SLE	5	1.44
OTHERS	39	11.21
Co-morbidity		
None	115	33.5
One	160	46
Two	57	16.38
≧ three	16	4.6
Haemodialysis Model		
HD Shift mode		
Morning	152	43.68
Afternoon	147	42.24
Night	48	13.79
Frequency on dialysis (week)		
2 times	11	3.16
3 times	335	96.26
>3 times	2	0.57
Hours / per session (HR)		
HR <3	1	0.29
3≦HR<3.5	25	7.20
3.5≦HR<4	255	73.49
4≦HR	66	19.02

Table 4-2. Characteristics of the HD subjects (cont')

Variable	N	%
Clinical Parameter		
Sleep medicine		
None	172	51.34
1	148	44.18
>2	15	4.48
EPO dosage per month		
None	3	0.87
EPO <10000U	89	25.95
10000U≦EPO<18000U	112	32.65
18000U≦EPO<26000U	91	26.53
26000U<EPO	48	13.99
Ferrous supply per month		
None	252	72.83
100mg	59	17.05
400mg	20	5.78
>400mg	11	3.18
IRLS		
0 point	157	48.61
1-10 point	87	26.93
11-20 point	29	8.98
21-30 point	26	8.05
31-40 point	24	7.43
BDI-II		
0-13 point	200	57.47
14-19 point	52	14.94
20-28 point	54	15.52
29-63 point	42	12.07

Table 4-3. Comparison of Good Sleepers and Poor Sleepers

Variables	Good Sleepers Global PSQI≦5		Poor Sleepers Global PSQI＞5		P
	N	(%)	N	(%)	
Basic Characteristic					
Age	59.02±14.51‡		61.19±13.90		0.178
Gender					0.004
Male	67	58.26	99	42.49	
Female	47	41.74	134	57.51	
Completed Education					
Illiterate	11	9.57	55	23.61	
Elementary school	45	39.13	79	33.91	
Junior high school	17	14.78	40	17.17	0.014
Senior high school	28	24.35	36	15.45	
College	7	6.09	17	7.30	
Graduate school	7	6.09	6	2.58	
Occupation status					
None	82	73.21	187	81.66	
Part-time	7	6.25	22	9.61	0.014 [a]
Full daytime	21	18.75	19	8.30	
Full nighttime	2	1.79	1	0.44	
Religion					
None	17	15.60	49	21.68	0.422
Taoism/ Buddhism	88	80.73	169	74.78	
Christian/ Catholic	44	3.67	8	3.54	
Marital status					
Single	9	7.89	23	9.91	
Married	90	78.95	174	75.00	0.867 [a]
Separated	1	0.88	3	1.29	
Widowed	10	8.77	26	11.21	
Divorced	4	3.51	6	2.59	

Table 4-3. Comparison of good sleepers and poor sleepers (cont')

Variables	Good Sleepers Global PSQI≦5		Poor Sleepers Global PSQI＞5		P
	N	(%)	N	(%)	
Family Income NT					
FI≦30	32	30.48	89	40.83	0.071 [a]
30＜FI≦60	41	39.05	89	40.83	
60＜FI≦90	19	18.10	20	9.17	
90＜FI≦120	10	9.52	11	5.05	
120< FI	3	2.86	12	4.12	
Time on dialysis (Years)	4.39±4.18		4.52±4.31		0.375
HD shift mode					
Morning	45	39.13	107	45.92	0.049
Afternoon	46	40.00	101	43.35	
Night	23	20.00	25	10.73	
Frequency on dialysis					
2 times	4	3.48	7	3.00	0.675[a]
3 times	110	95.65	225	96.57	
3 < times	1	0.87	1	0.43	
Hours / per session					
HR <3	1	0.88	0	0	
3≦HR<3.5	7	6.14	18	7.73	0.434[a]
3.5≦HR<4	82	71.93	173	74.25	
4≦HR	24	21.05	42	18.03	
Sleep medicine					
None	85	78.70	87	38.33	＜.001 [a]
1	23	21.30	125	55.07	
2≦	0	0	17	6.61	
EPO per month					
None	2	1.79	1	0.43	
EPO <10000U	36	32.14	53	22.94	0.187[a]
10000U≦EPO<18000U	34	30.36	78	33.77	
18000U≦EPO<26000U	24	21.43	67	29.00	
26000U<EPO	16	14.29	32	13.85	

Table 4-3. Comparison of Good Sleepers and Poor Sleepers (cont')

Variables	Good Sleepers Global PSQI≦5		Poor Sleepers Global PSQI＞5		P
	N	(%)	N	(%)	
Ferrous supply per month					
None	87	76.32	165	71.12	
100mg	15	13.16	44	18.97	0.731[a]
400mg	7	6.14	13	5.60	
400mg <	4	3.51	7	3.02	
Smoke					0.468
Yes	94	83.19	199	86.15	
No	19	16.81	32	13.85	
Coffee					0.249
Yes	92	82.88	203	87.50	
No	19	17.12	29	12.50	
RLS rating scale					
0	63	57.80	94	43.93	
1-10	34	31.19	53	24.77	0.003[a]
11-20	5	4.59	24	11.21	
21-30	3	2.75	23	10.75	
31-40	4	3.67	20	9.35	
BDI-II Scale					
0-13	86	74.78	114	48.93	
14-19	13	11.30	39	16.74	＜.001
20-28	9	7.83	45	19.31	
29-63	7	6.09	35	15.02	
Clinical and Biochemical					
Serum albumin (g/dl)	3.88±0.37		3.90±0.41		0.552
BUN(Pre-HD)(mg/dl)	72.98±17.00		73.71±20.02		0.738
Cr. (Pre-HD)(mg/dl)	10.82±2.86		10.88±2.76		0.833
Uric acid (mg/dl)	7.37±1.56		7.40±1.60		0.852
T-CHO (mg/dl)	178.50±41.15		177.34±49.67		0.830
TG (mg/dl)	161.23±138.69		161.44±114.75		0.988
URR (%)	74.39±5.91		74.08±7.26		0.692

Table 4-3. Comparison of Good Sleepers and Poor Sleepers (cont')

Variables	Good Sleepers Global PSQI≦5 N (%)	Poor Sleepers Global PSQI＞5 N (%)	P
Kt/V (Daugirdas)	1.46±0.24	1.49±0.25	0.324
Na (meq/L)	138.22±3.12	138.32±3.63	0.809
K (meq/L)	4.77±0.80	4.67±0.77	0.253
Ca (mg/dl)	9.42±0.82	9.61±0.87	0.059
P (mg/dl)	5.11±1.61	5.10±1.63	0.947
Ca*P	48.25±15.52	49.48±16.48	0.508
Ferritin (ng/ml)	595.36±555.55	597.52±643.67	0.976
Iron (ug/dl)	78.44±40.11	78.12±39.06	0.944
TIBC (ug/dl)	226.68±51.83	223.11±47.74	0.527
Iron/TIBC (%)	0.38±0.27	0.38±0.27	0.924
GOT (IU/L)	23.75±11.38	25.50±24.63	0.371
GPT (IU/L)	23.14±17.60	23.85±21.73	0.763
iPTH	278.08±326.66	214.75±269.69	0.058
Hematology			
RBC*106	3.49±0.84	3.45±0.79	0.661
Hb (g/dl)	10.59±1.37	10.47±1.42	0.452
Hct (%)	31.81±4.05	31.32±4.06	0.289
Physical			
Weight (Pre)	62.41±11.98	60.48±11.29	0.150
Weight (post)	59.48±11.28	57.81±10.94	0.188
Ultrafiltration	3.17±6.73	2.53±2.37	0.343
systolic BP(mmHg)	139.21±21.18	138.35±22.16	0.731
diastolic BP(mmHg)	78.06±9.62	77.39±9.77	0.548
Breath (time)	17.39±2.06	17.78±1.94	0.250
Heart rate	76.19±5.93	76.95±6.88	0.313

†t-test of the continuous variables, Chi-square of the categorical variables; [a]= p-value of Fisher'exact test ◦ ‡ mean ± SD.

Table 4-4. Multiple Linear Regression Models with PSQI score on HD patients.

	PSQI			
Variable	β	SE	t	P
Intercept	1.81	2.33	0.78	0.436
Age	0.04	0.02	1.99	0.047
Gender				
Male (reference)				
Female	0.49	0.50	0.97	0.331
Time on dialysis (Years)	0.08	0.05	1.47	0.143
HD Shift mode				
Morning (reference)				
Afternoon	-0.15	0.47	-0.32	0.745
Night	-0.29	0.82	-0.36	0.721
Number of Co-morbidity				
None (reference)				
1	0.34	0.50	0.69	0.492
2	1.17	0.67	1.74	0.082
3 ≦	0.77	1.07	0.72	0.471
Education status				
None and primary (reference)				
High school	0.76	0.55	1.38	0.168
College or above	0.80	0.81	0.99	0.320
Marital status				
Single (reference)				
Married	-0.37	0.82	-0.46	0.647
Separated	0.51	1.11	0.46	0.647
Widowed and divorced	-0.12	1.32	-0.09	0.926

Table 4-4. Multiple Linear Regression Models with PSQI score on HD patients. (cont')

	PSQI			
Variable	β	SE	t	P
Occupation status				
None (reference)				
Part-time	0.89	0.96	0.99	0.320
Full day-time	0.21	0.88	0.24	0.814
Full night-time	-1.53	2.29	-0.67	0.504
Family Income				
≦60 thousand (reference)				
>60 thousand	-1.14	0.54	-2.11	0.035
Smoke				
No (reference)				
Yes	-0.13	0.67	-0.19	0.846
Coffee				
No (reference)				
Yes	-0.30	0.67	-0.45	0.654
Sleep medicine				
No (reference)				
Yes	3.83	0.46	8.42	<0.001
RLS	0.10	0.03	3.20	<0.001
BDI-Ⅱ				
0-13 (reference)				
Mild (14-19)	1.68	0.66	2.56	0.011
Moderate (20-28)	2.13	0.66	3.24	0.001
Severe (>28)	2.54	0.76	3.34	0.001

R^2＝0.4084, Adj- R^2＝0.3598, P<0.0001

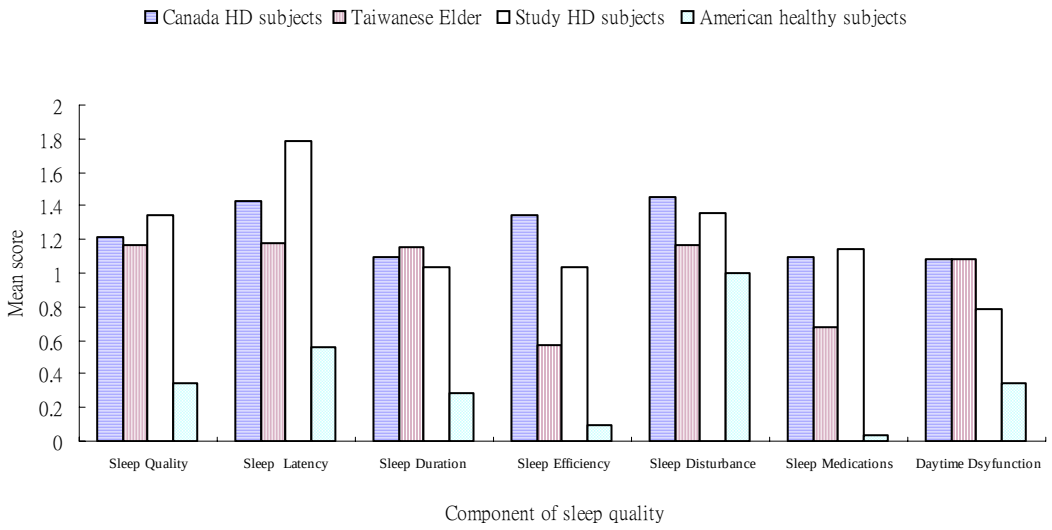

Figure 5-1. The mean scores in the seven components of the PSQI in our HD patients, Canadian HD patients [15], Taiwanese elder [76], and US healthy subject as normal control [66].

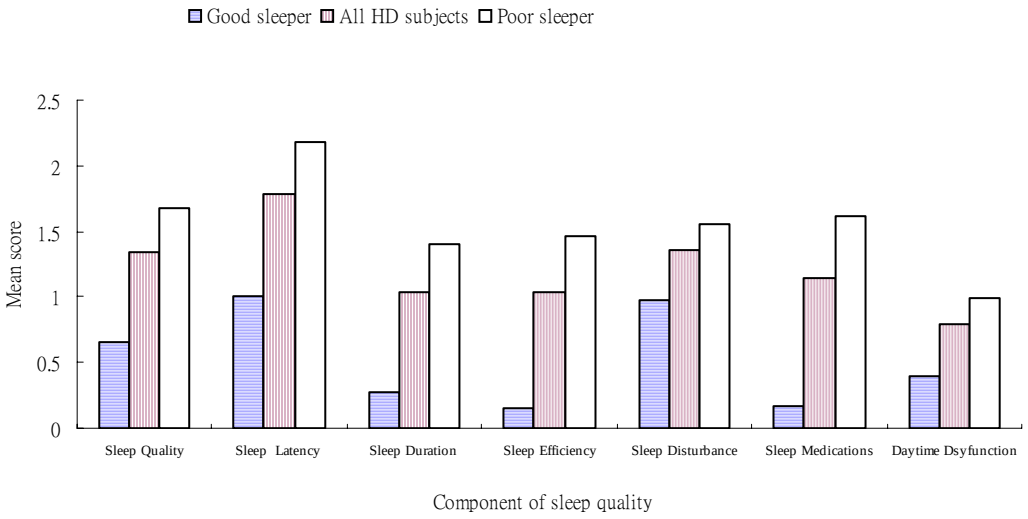

Figure 5-2. The mean score in the seven components of all HD subjects, ‘poor sleepers’, and ‘good sleepers’.

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