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Restless legs syndrome in end-stage renal disease patients on maintenance hemodialysis: Quality of life and sleep analysis

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Abstract

Vitamin D insufficiency, calcium/phosphate imbalance, iron deficiency, anemia, pregnancy, and end-stage renal disease (ESRD) are all thought to be involved in the pathogenesis of restless leg syndrome (RLS). The prevalence of RLS ranging from 6.6% to 83% has been reported in another study. It is one of the illnesses that affect the quality of life of ESRD patients on maintenance hemodialysis. Unfortunately, RLS has not received enough recognition and attention, and the underdiagnosed and undertreated rate can reach more than 10%. This study aimed to look at the sleep quality and quality of life of people with RLS who were on maintenance hemodialysis. The present study included 286 individuals on chronic dialysis. The International Restless Legs Syndrome Study Group Diagnostic Criteria and the International RLS Rating Scale were used as recommendations to diagnose and assess the severity of RLS. The Pittsburgh sleep quality index (PSQI) and the Short Form-36 Health Survey (SF-36) were employed to evaluate sleep quality and quality of life. All patients' biochemical and demographic data were reviewed, and statistical analyses were carried out. In conclusion, there were no statistically significant variations in demographic information or clinical and laboratory characteristics between RLS patients and those who did not have RLS. Specifically, among dialysis patients, those with RLS had higher PSQI and SF-36 ratings.

Keywords: Restless legs syndrome; End-stage renal disease; Maintenance dialysis; Quality of life; Quality of sleep

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1. Introduction

Restless legs syndrome (RLS) is a prevalent sensory-motor problem in hemodialysis (HD) patients that causes sleep disruptions, harms the quality of life, and has been linked to increased morbidity and mortality in patients on maintenance hemodialysis. However, no consistent results have been obtained regarding the relationship of RLS with quality of life and sleep quality in patients on maintenance hemodialysis. There was an extensive range in the outcomes of prior investigations due to complicated etiology, pathophysiology, reference standards, race, regional disparities, study technique discrepancies, and diversity.

Despite the significant frequency of sleep disruption in MHD patients, the causes remain unclear and are likely multifaceted. RLS has been shown to harm many elements of quality of life and sleep quality, which may trigger sadness and anxiety[1]. Furthermore, studies have found that premature dialysis termination is linked to RLS symptoms, poor transferrin saturation levels due to iron insufficiency, and sleep start delay[2]. In addition, RLS was associated with an increased risk of death, and the relationship was somewhat reduced when controlling for sleep-related disorders[1,3,4]. Furthermore, after correcting for comorbidities, demographic factors, and possible clinical confounders, severe restless legs symptoms were independently related to elevated mortality risk[5]. A recent study by Kambampati *et al.*[6] has shown that sleep fragmentation and sleep deprivation induced by RLS may contribute to cardiovascular problems and inflammatory infections, frequently resulting in a poor prognosis in dialysis patients. Complete analyses of RLS-related quality of life and sleep disruption, which may lead to specialized treatment, are time-consuming and difficult. We anticipated that RLS is a prevalent illness in these individuals because of concomitant conditions, such as iron metabolism disorders, dialysis-related variables, systemic inflammation, peripheral neuropathy, diabetes mellitus, and electrolyte imbalance[7]. In general, the purpose of this study was to investigate the link between LRS and common sleep disorders, as well as the possible consequences on quality of life parameters[2]. RLS treatment improves clinical outcomes in dialysis patients. The general measures include reduced possible aggravating variables such as living standards, medical issues, and drugs[8]. The revious research has suggested that a dopamine receptor agonist treatment drug might help with RLS symptoms[4].

2. Methods

2.1. Participants

From September 2012 to September 2017, 286 patients with end-stage renal disease (ESRD) on maintenance hemodialysis participated in our research at the Affiliated Hospital of Weifang Medical University. The Ethics Committee approved the protocol for the study of Weifang Medical University's Affiliated Hospital (wyfy-2022-ky-183), and all subjects provided informed consent. Inclusion criteria of the present study are as follows: (i) Patients aged from 18 years to 80 years; (ii) those who met the diagnostic criteria for chronic renal failure with uremia; (iii) those who received maintenance hemodialysis 3 times/week, 4 h per time and for a period of over 3 months; (iv) those who used the same hemodialysis and dialysis; and (v) those who were in stable condition during the study. Exclusion criteria of then present study are as follows: (i) Those who had disturbance of consciousness, severe dysarthria, aphasia and cognitive disorders; (ii) those who had severe auditory or visual impairment, and physical frailty that prevented interview attendance; (iii) those who had severe comorbidities (e.g., heart disease, lung disease, liver disease, kidney dysfunction, nutritional deficiency, electrolyte disorder, severe endocrine and infectious diseases, neuropsychiatric complications, and mental illness) that could affect follow-up assessment; (iv) those who were using antipsychotics, dopamine agonists, and nerves nutritional drugs; (v) those with a history of central nervous system disease (such as tumor, trauma, hydrocephalus, Parkinson's disease, dementia), malignancies, human immunodeficiency disease and opportunistic infections; (vi) those who did not provide comprehensive records and lost to follow-up; and (vii) those who refused to participate and sign the written consent. Figure 1 shows the flow chart of study and patient selection.

2.2. Clinical assessments

2.2.1. Patient characteristics

We collected the basic demographic parameters related to age, gender, smoking, alcohol intake, history of renal disease, and comorbid disease (chronic glomerulonephritis, diabetic mellitus, and hypertension), information regarding dialysis therapy (such as age at initiation, duration of chronic kidney disease, time of dialysis, the delivered dose of dialysis [Kt/V], dry weigh, ultrafiltration volume, pre/post-dialysis mean systolic/diastolic blood pressure [BP]), biochemical parameters (blood urea nitrogen [BUN], creatinine, albumin, hemoglobin, ferritin, serum iron, total iron-binding capacity [TIBC], calcium, phosphorus, Ca × P product, intact parathyroid hormone [i-PTH], and C-reactive protein [CRP], β2-MG) in the two groups with or without RLS.

2.2.2. International Restless Legs Syndrome Study Group (IRLSSG) criteria for the diagnosis of RLS

The RLS patients were diagnosed according to the criteria of the IRLSSG[9,10]. The four minimal criteria include: (i) Urge to move the legs, usually accompanied or caused by uncomfortable leg sensations; (ii) temporary relief with movement, partial or total relief from discomfort by walking or stretching; (iii) onset or worsening of symptoms at rest or inactivity, such as when lying down or sitting; and (iv) an aggravation or onset of symptoms in the evening or at night. To assess the severity of RLS, we used the IRLSSG severity scale. Severity classification is as follows: Mild (1 – 10 points), moderate (11 – 20 points), severe (21 – 30 points), and very severe (31 – 40 points).

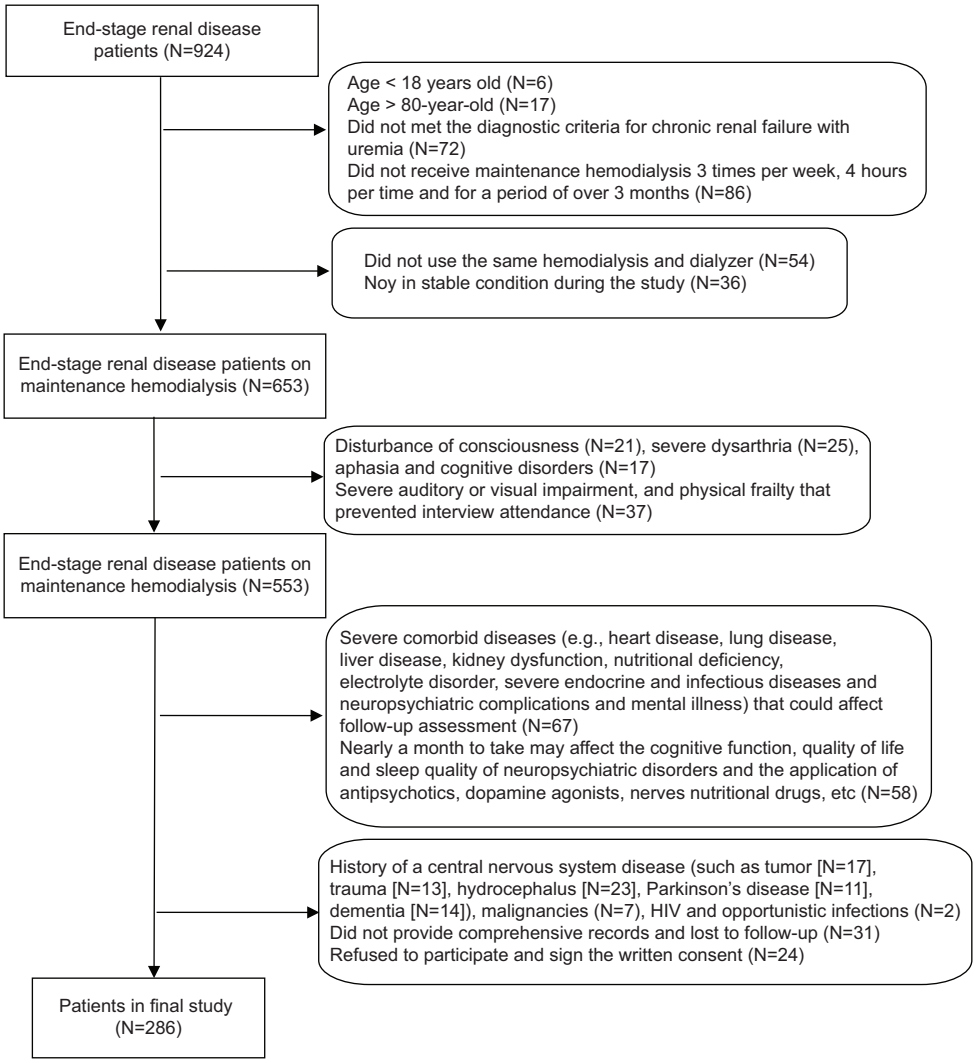

Figure 1. Flow chart of study search and selection. "→" indicates exclusion criteria.

2.2.3. Short form 36 (SF-36) health survey

The SF-36 was used to assess quality of life. The data from 36 items in eight subscales were integrated to measure the nutrition-associated quality of life in eight dimensions: Physical functioning, emotional role, physiological pain, general health, vitality, social functioning, and mental health. The SF-36 total score ranges from 0 to 100. The higher the score, the greater the quality of life; otherwise, the worse.

2.2.4. Assessment of sleep quality

The Pittsburgh sleep quality index (PSQI) is a method for measuring sleep quality. Seven component ratings ranging from 0 to 3 are generated from 19 individual items. PSQI may be classified into seven factors: subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, sleep disruption, usage of sleep medication, and daytime dysfunction. The total scores for these seven components result in a single global score. Lower ratings indicate better sleep quality. A global score of 5 or higher implies clinically severe sleep disruption.

2.3. Statistical methods

The SPSS 20.0 statistical program was used to analyze the data. The mean, standard deviation, or median (interquartile range) represent numerical data, while percentages are used to express data of categorical variables. To investigate differences between continuous variables, the Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed variables were employed. Correlation analysis also be performed to better describe the RLS-sleep or RLS-quality of life association. In contrast, the Fisher's exact test was used to analyze correlations between categorical variables. $P < 0.05$ indicates that the difference was statistically significant.

3. Results

The demographic data and clinical analysis results of the 286 patients on hemodialysis are shown in Table 1. Of the total, 41 patients (14.34%) were diagnosed with RLS with a male/female ratio of 16/25. Chronic glomerulonephrites is the primary disease in 155 patients (54.2%). The RLS severity score was 14.39 ± 9.75; there were 8 mild cases (19.51%), 25 moderate cases (60.98%), 6 severe cases (14.63%), and 2 very severe cases (4.88%). There was no significant association between RLS and gender, mean age, body mass index (BMI), smoking, drinking, mean age at the initiation of hemodialysis, hemodialysis duration, primary disease, and drug usage ($P > 0.05$).

The means of laboratory data, including hemoglobin, serum creatinine, uric acid, plasma albumin, calcium, phosphorus, magnesium, i-PTH, ferritin, and transferrin saturation, are shown in Table 2. No significant difference between the two groups (RLS-positive and RLS-negative patients) regarding all the laboratory data, including pre/post-dialysis mean systolic/diastolic BP, BUN, creatinine, albumin, hemoglobin, ferritin, iron saturation, iron, TIBC, calcium, phosphorus, Ca×P product, i-PTH, CRP, and β2-MG, was observed. There was a significant relationship between RLS severity and all SF-36 subscale scores, except the subscales "physical component score," "social functioning," and "general health" ($P < 0.005$). The RLS-negative patients had higher scores on the subscales physical functioning ($P = 0.019$), role limitations due to physical health ($P = 0.018$), pain ($P = 0.011$), mental component score ($P = 0.009$), energy/vitality ($P = 0.009$), vitality ($P = 0.005$), emotion ($P = 0.027$), and mental health ($P = 0.010$) than those RLS-positive patients (Table 3). Sleep disorders were considered more common in RLS-positive patients. These disorders included total PSQI global score, subjective sleep quality, sleep latency, duration of sleep, habitual sleep efficiency, and sleep disturbances ($P < 0.05$). However, there was no difference in the use of sleep medication and daytime dysfunction ($P > 0.05$), as shown in Table 4 and Table 5.

4. Discussion

Even though investigations into the etiopathogenesis of RLS have been conducted for many years, RLS is regarded as a complex condition in which genetic background, environmental variables, and gene-environment interactions are more likely to cause illness. Thousands of genetic studies have shown the hereditary variability of the illness and RLS is now considered a complicated congenital disorder. Large-scale genome-wide association study

Table 1. Clinical characteristics of patients on hemodialysis with and without RLS

	RLS	Non-RLS	*P*-value
Sex (female/male)	25/16	132/113	0.3979
Mean age (years)	56.37±14.35	54.64±15.13	0.4954
BMI (mean±SD)	22.58±3.41	23.61±3.62	0.090
Smoking	22 (53.66%)	141 (57.55%)	0.217
Drinking	23 (56.10%)	145 (59.18%)	0.1380
Mean age at the initiation of hemodialysis (years)	48.26±11.26	51.26±13.17	0.1698
Hemodialysis duration (years)			
≤5	25 (60.98%)	153 (62.45%)	0.8571
5–10	10 (24.39%)	66 (26.94%)	0.7324
≥10	6 (14.63%)	26 (10.61%)	0.4496
Primary disease			
Chronic glomerulonephritis	18 (43.90%)	137 (55.92%)	0.1529
Diabetic nephropathy	7 (17.07%)	29 (11.84%)	0.3459
Hypertensive nephropathy	9 (21.95%)	35 (14.29%)	0.2080
Others	7 (17.07%)	44 (17.96%)	0.8909
Drug			
Vitamins	17 (41.46%)	71 (28.98%)	0.1089
Anti-osteoporosis	27 (65.85%)	167 (68.16%)	0.7695
Erythropoietin and iron supplements	31 (75.61%)	203 (82.86%)	0.2655

BMI: Body mass index; RLS: Restless legs syndrome. Categorical variables are expressed as percentage while continuous variables are expressed as mean±standard deviation. *P<0.05

Table 2. Prevalence rate of RLS in maintenance hemodialysis patients from other studies

Study	Country	Prevalence rate (%)	Study	Country	Prevalence rate (%)
Xiao *et al.* 2017[1], Lin *et al.* 2013 (Taiwan)[18]	China	14.5%, 25.3%	Soumeila *et al.* 2015[36]	Maroc	41.7%
Jaber *et al.* 2011[19], Stefanidis *et al.* 2015[35],	USA	15.6%, 40%	Wali *et al.* 2015[37]	Saudi Arabia	19.4%
Tuncel *et al.* 2011[28], Demircioglu *et al.* 2015[38], Örsal *et al.* 2017[39], Kaya *et al.* 2015[44], Dikici *et al.* 2014[53]	Turkey	12%, 15.6%, 15.9%, 41.53%, 45.9%	Merlino *et al.* 2012[30], La Manna *et al.* 2011[31], Pizza *et al.* 2012[32], Baiardi *et al.* 2017[41]	Italy	19%, 31%, 32%, 36.7%
Esteve *et al.* 2017[40]	España	21.21%	Lee *et al.* 2013[33]	Canada	26%
Cengić *et al.* 2012[29]	Bosnia and Herzegovina	20.5%	Salman *et al.* 2011[34]	Allepo, Syria	20.3%
Neves *et al.* 2017[43]	Brazil	28.7%	Rohani *et al.* 2015[46]	Iran	37.4%
Higuchi *et al.* 2015[45]	Japan	22%	Beladi-Mousavi *et al.* 2015[47], Chavoshi *et al.* 2015[48]	IR Iran	15.8%, 31.7%
Bathla *et al.* 2016[50]	India	5.2%	De Santo *et al.* 2010[52]	Egypt	42%
Giannaki *et al.* 2017[49]	Cyprus	27.06%	Stefanidis *et al.* 2013[51]	Greece	26.6%

discovered apparent genetic risk variations replicated in 23 genomic locations[11]. Furthermore, a study showed that heritability contributed to RLS with common genetic variations amounting to 19.6% (single-nucleotide polymorphism [SNP]-based heritability), indicating the importance of these variants in RLS susceptibility[12]. In terms of etiological insights, numerous mechanisms, such as brain iron shortage, dopamine dysregulation, and hyper-glutamatergic condition, have been found and postulated to play a crucial role in pathophysiologies[13-14]. The previous studies have been conducted to determine the risk factors for RLS in patients on maintenance hemodialysis, but the results have been inconsistent, varied greatly, and have remained contentious. Unlike previous reports, we have not found an association of sleep quality index with serum creatinine, serum urea, cystatin-C, hemoglobin, and hematocrit levels, which might be attributed to the erythropoietin therapy and hemodialysis procedure. The main strengths of this study include the large number of patients studied and the comprehensive review process.

In our investigation, we found no change in parathyroid hormone (PTH) levels in two groups. The previous research has shown conflicting outcomes. In a prior study[15,16], PTH levels were observed to be lower in ESRD patients with RLS than in those without RLS. Recent investigations, on the other hand, have found that PTH is an independent risk factor[17], which is corroborated by the discovery that parathyroidectomy improved RLS in ESRD patients in one study[18]. Nonetheless, several research revealed that there is no link between PTH and RLS in ESRD patients. As a result, investigations involving larger sample size are needed to determine the link between PTH and RLS in ESRD patients[19,20].

Other risk factors for RLS include marital status, educational level, work status, dialysis type, dialysis frequency, and history of renal transplantation. However, we did not examine if there were any significant variations in these potential risk variables in the current subject population. Future research into the effects of these intervention variables on RLS-positive and RLS-negative patients is required. Studies on its relationship with laboratory data produced inconsistent findings. We found no link between hemoglobin, ferritin levels, and the Kt/V index in RLS patients. These findings were consistent with those of other investigations[8]. Sleep difficulties, depression, and polyneuropathy are known to follow these individuals and impact their quality of life, adherence to therapy, and overall health[4,5]. Serum albumin, i-PTH level, hemoglobin, urea, phosphorus, calcium, Kt/V index, and dialysis time have all been proven to have a significant impact on RLS patients' quality of life[15,17]. Furthermore, no correlation was detected between RLS and hematocrit, serum sodium, serum potassium, serum magnesium, Ca×P product, serum creatinine, BUN, serum albumin, CRP, uric acid, serum β2-MG, or iron metabolism markers.

Quality of life dimensions such as SF-36 total score, physical and mental component scores, bodily pain, general health perceptions, vitality, role functioning, emotion, and maintenance hemodialysis (MH) were significantly linked with RLS patients in our study. Sleep issues are widespread in ESRD patients, especially those with RLS, and contribute

Table 3. Laboratory and clinical indicators data of hemodialysis patients with and without RLS

	RLS	Non-RLS	*P*-value
Hemoglobin (g/dL)	105.34±15.12	101.86±17.32	0.2268
Hematocrit (%)	32.35±7. 12	33.65±6. 87	0.2655
Serum sodium (mmol/L)	134.24±13.68	137.15±10. 45	0.1168
Serum potassium (mmol/L)	4.46±0.72	4.53±0.68	0.5457
Serum magnesium (mmol/l)	1.15±0.24	1.12±0.21	0.4078
Serum phosphate (mmol/L)	4.46±0.72	4.53±0.68	0.5457
Serum calcium (mmol/L)	2.14±0.23	2.17±0.25	0.1515
Ca×P product (mg^2/dL^2)	51.43±15.12	52.95±13.76	0.5192
Serum creatinine	785.36±248.85	790.78±243.61	0.8955
BUN (mmol/L)	24.86±8.34	23.12±9.61	0.2756
Serum albumin (g/dL)	38.74±3.15	39.53±4.82	0.3118
i-PTH (pg/mL)	312.45±246.87	326.87±231.62	0.7150
Serum β2-MG (g/dL)	21.56±6.73	22.14±7.34	0.6361
CRP (mg/L)	13.86±4.57	12.43±5.81	0.1348
Uric acid (μmol/L)	345.53±101.67	336.41±117.82	0.6407
Ferritin (μg/L)	386.86±254.31	374.93±267.87	0.7906
Transferrin saturation (%)	24.85±3.14	26.13±4.26	0.0667
Iron saturation (%)	25.44±10.07	24.26±9.91	0.4820
Iron (μmol/L)	51±24	53±21	0.5810
TIBC (μmol/L)	223.12±42.38	217.86±48.24	0.5118
Kt/V	1.41±0.21	1.46±0.23	0.1933
Dry weight (kg)	61.58±9.76	58.13±11.24	0.0651
Ultrafiltration volume (kg)	1.62±1.13	1.57±1.34	0.8215
Pre-dialysis mean systolic BP (mmHg)	138.4±12.8	136.7±15.4	0.4810
Pre-dialysis mean diastolic BP (mmHg)	88.7±7.3	85.7±10.1	0.3922
Post-dialysis mean systolic BP (mmHg)	135.5±10.2	132.4±12.3	0.1277
Pre-dialysis mean diatolic BP (mmHg)	78.3±6.9	75.7±8.5	0.0642

β2-MG: β2-microgloblin; BUN: Blood urea nitrogen; CRP: C-reactive protein; i-PTH: intact parathyroid hormone; RLS: Restless legs syndrome; TIBC: Total iron binding capacity; Categorical variables are expressed as percentage while continuous variables are expressed as mean±standard deviation. *P<0.05

to a worse quality of life. In this patient population, the severity of RLS during sleep has been connected to an increased risk of cardiovascular and cerebrovascular illness and an increased risk of mortality[21-25]. RLS was linked to less peaceful nocturnal sleep, daily somnolence, and excessive daytime drowsiness, which led to symptoms of other sleep disorders, including insomnia, and lower overall sleep quality. Cederberg discovered that anxiety was much worse in individuals with MS and RLS, as well as higher levels of weariness and fear, compared to patients without concomitant RLS, which is similar to those with optic neuromyelitis[26].

Iron has been utilized to treat RLS in the general population. L-dopa and dopamine agonists are medications used to treat RLS[5,24,25]. RLS treatment aims to alleviate symptoms while also increasing sleep quality and quantity[26-28,42]. Non-pharmacologic treatment (for example, exercise training) or iron deficiency repair, common in ESRD, may be an effective therapy for people with moderate or occasional symptoms. Pharmacologic therapy, on the other hand, is frequently necessary for individuals with more severe illnesses.

Several limitations should be addressed when interpreting our findings. The most significant disadvantage of this study is the absence of metabolism gained from information on pharmaceuticals other than those that show the role of iron metabolism. Second, the sample size in this study is limited. Third, even after accounting for confounding factors, we cannot rule out the potential that unmeasured factors may explain some of our findings.

Table 4. SF-36 scores for RLS and non-RLS patients

	RLS	Non-RLS	*P*-value
Physical component score	42.56±12.91	45.86±16.18	0.2157
Physical functioning	62.31±18.62	71.14±22.76	0.0192*
Role physical	44.47±24.12	56.76±31.53	0.0179*
Bodily pain	51.43±23.56	64.17±30.49	0.0113*
General health	44.83±19.47	48.76±23.49	0.3114
Mental component score	45.21±11.47	51.65±14.84	0.0090*
Vitality	52.84±19.35	63.87±23.52	0.0050*
Social functioning	58.17±22.74	62.34±25.81	0.3314E
Emotion	40.32±32.74	54.65±39.15	0.0270*
Mental health	62.51±16.34	71.32±20.75	0.0101*

RLS: Restless legs syndrome; SF-36: Short Form-36. Categorical variables are expressed as percentage while continuous variables are expressed as mean±standard deviation. *P<0.05.

Table 5. PSQI scores for RLS and non-RLS patients

	RLS	Non-RLS	*P*-value
Sleep quality	1.76±0.75	1.43±0.61	0.0049*
Sleep latency	2.18±1.22	1.57±1.18	0.0025*
Sleep duration	1.28±0.87	1.01±0.61	0.0149*
Habitual sleep efficiency	1.47±0.72	1.24±0.45	0.0065*
Sleep disturbance	2.31±0.85	2.02±0.57	0.0057*
Use of sleep medication	1.28±1.14	1.19±0.92	0.5766
Daytime dysfunction	1.12±0.93	0.95±0.76	0.2011
PSQI global score	9.83±5.15	7.43±4.62	0.0027*

PSQI: Pittsburgh sleep quality index; RLS: restless legs syndrome; SF-36: Short Form-36. Continuous variables are expressed as mean±standard deviation. *P<0.05

Finally, whether additional variables such as weariness, sadness, patient disease uncertainty, nursing care, social and family support, and limited diets impact sleep quality and quality of life remain unknown.

5. Conclusions

This study found that RLS is a significant symptom of dialysis patients. Since the intensity of restless legs symptoms in ESRD patients is linked to lower sleep quality, impaired physical functioning and lifestyle standards, and increased mortality risk, management and treatment of this syndrome necessitates a long-term investment. Furthermore, RLS patients had poor sleep quality, particularly in subjective sleep quality, sleep latency, sleep duration, sleep efficiency, and daytime dysfunction. Moreover, RLS patients have a lower quality of life in terms of physical functioning, role restriction, pain, vitality, emotion, and mental health.

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Conflict of interest

The authors declare that they have no competing interests

Author contributions

Conceptualization: Ning Xu
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Writing – original draft: Ning Xu
Writing – review & editing: Ning Xu

All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee approved the protocol for the study of Weifang Medical University's Affiliated Hospital (wyfy-2022-ky-183), and all subjects provided informed consent.

Consent for publication

Consent was obtained from all the participants.

Availability of data

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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