

## Restless Legs Syndrome: Associated Risk Factors in Hemodialysis Patients

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### Abstract

**Background:** Restless legs syndrome (RLS) may be associated with increased morbidity and mortality among end-stage renal disease (ESRD) patients; however, it is a disorder that is neglected in dialysis centers.

**Objectives:** The goal of this study was to investigate the clinical factors associated with RLS among ESRD patients.

**Patients and Methods:** This cross-sectional study was conducted on ESRD patients undergoing maintenance hemodialysis (HD) in three HD centers in Ahvaz city in Southwest Iran. Blood samples were obtained prior to a dialysis session to check the routine laboratory test results and assess the adequacy of dialysis. The presence of RLS was assessed by using the international RLS study group (IRLSSG) diagnostic criteria. The IRLSSG rating scale was also used to evaluate the severity of the RLS symptoms.

**Results:** Of the 139 HD patients enrolled in this study, 60 were female (43.2%) and 79 were male (56.8%), with a mean age of  $51.82 \pm 13.31$  years. The prevalence of RLS was 15.8% (22 patients), with 50% of them (11 patients) having severe or very severe symptoms. There was a significant relationship between RLS and longer durations of dialysis ( $P < 0.001$ ). The mean level of serum ferritin was lower in patients without RLS, but it was not significant ( $P = 0.065$ ). No significant differences were found according to age, gender, dialysis shifts, and hemoglobin (Hb) level among patients with and without RLS.

**Conclusions:** We conclude that a significant percentage of ESRD patients undergoing maintenance HD have severe or very severe RLS symptoms. The presence of RLS is associated to longer durations of dialysis.

**Keywords:** Restless Legs Syndrome, End-Stage Renal Disease, Chronic Kidney Diseases, Hemodialysis, Risk Factors, Sleep Disorders

## 1. Background

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an unpleasant sensation in the legs and, consequently, the patients' urge to move the lower extremities (1). These symptoms usually emerge at night or at times of rest, leading to sleep disturbances (2, 3), which are relieved by movement (4).

The prevalence of RLS in the general population varies widely depending upon the population surveyed. For example, it is reported that the prevalence of RLS in Europe and North America is 5 - 20% and in Asia less than 4% (5-7).

RLS occurs in both men and women at any age; however, it seems that the incidence of RLS is approximately twice as high in women. Several studies have shown that the symptoms typically become more frequent and last longer with age, from 3% of participants aged 18 to 29, 10% for those aged 30 to 79, and up to 19% for those aged 80 or older. In most people with moderate to severe RLS, the condition causes exhaustion, daytime fatigue, and depression, and activities of daily living are strongly affected as a result of the condition (1, 2, 4).

In most cases, RLS is a primary idiopathic disorder with unknown causes, but it can also be associated with a number of medical disorders, including diabetes mellitus, iron deficiency, multiple sclerosis, Parkinson's disease, rheumatic disease, and venous insufficiency (8-11).

End-stage renal disease (ESRD), which is defined as an irreversible and advanced loss of renal function requiring renal replacement therapy, appears to be another risk factor for the occurrence or worsening of RLS (12-15). It is also suggested that RLS may be associated with increased morbidity and mortality among ESRD patients (16-18). However, it seems that the importance of RLS and its treatment are neglected issues in dialysis centers (19).

The mechanism of increased mortality among ESRD patients is not well understood, but it may be due to poor compliance with therapy, impaired health-related quality of life, depression, and the psychological consequences of recurrent sleep disruption in these patients (19).

Although many studies about the epidemiology, causes, and treatment of primary RLS in the general popula-

tion have been conducted, researches about secondary RLS, especially among patients with ESRD which is a life-threatening disease with significant complications, are limited and give conflicting results (12-15, 20, 21); therefore, further studies about these patients are needed.

## 2. Objectives

The goal of this study was to investigate the frequency of RLS among patients with ESRD undergoing maintenance hemodialysis in Khuzestan, Iran, and to evaluate its relationship with hemoglobin (Hb), ferritin, calcium, phosphate levels, disease duration, and the Kt/V index among these patients.

## 3. Patients and Methods

### 3.1. Study Subjects

All ESRD patients under regular hemodialysis at three dialysis centers in the Ahvaz Jundishapur university hospitals between April 2011 and January 2013 were included in this study. Patients were included if they had undergone regular hemodialysis and their Glasgow coma scale score was equal to 15. The protocol was approved by the ethics committee of the chronic renal failure research center's Ahvaz Jundishapur university of medical sciences. The aim of the study was explained to the participants and written informed consents were obtained. It was decided to exclude patients with less than three months' dialysis treatment, patients with severe infections, and patients who refused to participate or who were unable to communicate before the study commenced.

### 3.2. Study Design

Of the 180 HD patients enrolled in the study, 41 were excluded. Twenty patients refused to participate, 11 patients had less than three months of dialysis treatment, five patients could not speak the Persian language, and five patients were excluded because of psychiatric disorders. The demographic information of ESRD patients, such as age, gender, weeks on dialysis, and shift of HD, was assessed by reviewing the patients' files.

Blood samples were obtained from patients who participated in the study prior to a dialysis session to check the routine laboratory test results, including calcium, phosphorus, Hb, serum ferritin, and alkaline phosphatase. In addition, to assess the adequacy of dialysis, blood urea nitrogen (BUN) before and after hemodialysis and ultrafiltration rate were also measured, and according to these parameters, the urea reduction ratio (URR) and Kt/V were calculated.

The presence of RLS was assessed by using the international RLS study group (IRLSSG) diagnostic criteria, and these questionnaires were conducted through face-to-face interviews by one of the investigators (22, 23) (Box 1). Four questions proposed by the IRLSSG for diagnosing RLS were used. Patients who answered "yes" to all four of these essential questions were classified as "RLS positive" and were asked to answer 10 questions on the IRLSSG rating scale (22, 24). The IRLSSG rating scale was also used to evaluate the severity of RLS symptoms.

### 3.3. Hemodialysis Methods

All subjects received hemodialysis by Fresenius machines in three four-hour shifts, with the morning shift starting at 8 AM, the afternoon shift starting at 3 PM, and the evening shift starting at 8 PM. Regular hemodialysis is defined as hemodialysis three or four times a week for at least three months by using semi-synthetic (cellulose diacetate) or synthetic (polysulfone) dialysis membranes and bicarbonate buffered dialysate. The rate of blood flow was maintained at 250 - 400 mL/minute and the dialysate flow rate was 500 mL/minute.

### 3.4. Statistical Analysis

The chi-square test was used for the categorical variables and the t-test was used for continuous variables. The continuous data are presented as mean  $\pm$  standard deviation. A P Value < 0.05 was considered statistically significant. In a forward manner, multivariate logistic regression analysis was used to evaluate factors independently predicting the presence of RLS. Odds ratio (OR) and 95% confidence interval (CI) were also calculated. All analyses were performed using SPSS version 17 software.

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#### Box 1. Essential Diagnostic Criteria for RLS

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##### Criteria

1. An irresistible urge to move the legs, usually accompanied by an unpleasant sensation in the legs (these symptoms are described as creeping, crawling, tingling, aching, burning, itching, or cramping).
  2. The urge to move or unpleasant sensations beginning or worsening during periods of rest or inactivity such as lying or sitting.
  3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
  4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.
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**Table 1.** Demographic and Laboratory Variables Between ESRD Patients with RLS and Without RLS<sup>a</sup>

Demographic and Laboratory Data	All Patients (n = 139)	RLS (n = 22)	No RLS (n = 117)	P Value
Age, y <sup>b</sup>	51.82 ± 13.316	51.91 ± 13.575	51.80 ± 13.326	.973
<b>Gender</b>				.492
Female	60	11	49	
Male	79	11	68	
<b>Weeks on dialysis<sup>b</sup></b>	126.24 ± 120.542	211.45 ± 151.736	110.22 ± 107.154	< .001
<b>Shift of dialysis</b>				.959
Morning	72	12	60	
Afternoon	53	8	45	
Evening	14	2	12	
<b>Hb, g/dL<sup>b</sup></b>	10.235 ± 1.866	10.324 ± 1.596	10.219 ± 1.916	.814
<b>Calcium, mg/dL<sup>b</sup></b>	8.43 ± 1.403	8.543 ± 1.179	8.409 ± 1.4438	.690
<b>Phosphate, mg/dL<sup>b</sup></b>	5.634 ± 1.795	5.567 ± 1.592	5.646 ± 1.835	.853
<b>Ferritin, ng/mL<sup>b</sup></b>	602.167 ± 265.485	713.000 ± 211.812	578.203 ± 270.993	.065
<b>Kt/V<sup>b</sup></b>	1.24 ± 0.03	1.25 ± 0.03	1.24 ± 0.04	.613
<b>URR, %<sup>b</sup></b>	66.02 ± 0.8	66.32 ± 1.1	65.97 ± 0.82	.087

Abbreviations: Hb, Hemoglobin; Kt/V is a number used to quantify hemodialysis (K, dialyzer clearance of urea; t, dialysis time; V, volume of distribution of urea, approximately equal to patient's total body water); URR, urea reduction ratio.

<sup>a</sup>P < 0.05 was considered a statistically significant difference.

<sup>b</sup>Values are presented as mean ± SD.

#### 4. Results

Data from 139 patients were analyzed. The mean age was 51.82 ± 13.31 years and there were 60 females (43.2%) and 79 males (56.8%). The mean duration of the patients' dialysis was 126.24 ± 120.542 weeks. RLS was found in 15.8% of the patients in this study. According to the IRLSSG rating scale (22), symptom severity in the RLS group was mild in three patients (13.63%), moderate in eight patients (36.36%), severe in nine patients (40.9%), and very severe in two patients (9.09%). The demographic and biochemical characteristics of the patients with and without RLS is compared in Table 1. Compared to patients with RLS, the mean level of ferritin was lower in patients without RLS, but this difference was not statistically significant (P Value = 0.065).

The duration of dialysis was significantly longer among patients with RLS compared to patients without RLS (P Value < 0.001). The duration of dialysis was defined as the number of weeks in which the patients had been under continuous dialysis.

No significant associations were found between RLS and age, gender, dialysis shift, and levels of Hb, calcium, phosphate, URR, and Kt/v (P Value > 0.05). We built multivariate logistic regression models with the presence of RLS as the dependent variable and several covariables, such as age, gender, duration of dialysis, and levels of calcium, phosphate, Hb, ferritin, URR, and Kt/V as independent variables. The regression analysis revealed that a longer duration of dialysis was the only independent

factor associated with the presence of RLS while controlling for other variables (OR = 1.006, 95% CI = 1.002 - 1.009, P Value = 0.001).

#### 5. Discussion

The prevalence of RLS among our HD patients was 15.8%, with 50% of them having severe or very severe symptoms, which can have a great influence on their quality of life. The frequency of RLS in our study differs from the results of previous studies on ESRD populations in other countries. For example, the prevalence of RLS among ESRD patients in Korea is 28%, Japan 23%, and in India 6.6%, respectively (4, 25, 26). These variations of RLS prevalence across different populations might be due to racial differences, language, culture, and the genetics of the studied populations, small study samples, environmental factors, as well as different understandings of common diagnostic criteria (4).

Furthermore, previous studies on the Iranian ESRD population have reported different RLS prevalence, for example, 8% (27) and 32% (28). These variations suggest differences in inclusion and exclusion criteria of the studies or in study strategies for using the IRLSSG criteria to diagnose RLS (i.e. face-to-face interviews or self-administrated questionnaires), different sample sizes in the studies, or different population study characteristics such as mean age, female gender percentile, mean dialysis duration,

dialysis strategies, the number of centers included in the study and different biochemical markers (24).

The pathogenesis of RLS among patients with ESRD is not understood. However, it is reported that some factors, including anemia, iron deficiency and elevated serum calcium, may predispose ESRD patients to develop RLS. In addition, central nervous system abnormalities and peripheral neuropathy, secondary to uremia or the underlying cause of ESRD (such as diabetes), may also contribute. The relationship between iron deficiency and ESRD-associated RLS has been suggested by some studies. Iron deficiency in ESRD patients may lead to RLS due to some possible underlying mechanisms, including anemia and alterations of dopamine metabolism in the central nervous system.

Although in our study, the ferritin level tended to be elevated among patients with RLS, this was not statistically significant, nor was it in other studies (4, 12, 14, 26, 29-33).

The serum ferritin level is not a good predictor for iron status among ESRD patients because it is also a positive acute phase reactant protein (34).

In our study, a significant relationship was found between the duration of dialysis and the presence of RLS. This close relationship suggests that the duration of dialysis may be a risk factor for developing RLS. Similar to our study, a few studies have found a relationship between dialysis duration and the presence of RLS (35-37), but this finding has not been confirmed by other studies (4, 38-40)

We found no association between the presence of RLS and the mean age of ESRD patients, similar to the results of previous studies (12, 31, 32, 41), although some studies have conflicting results (4, 26).

In contrast to the results of our study, some investigations have shown that RLS is more prevalent in uremic females (12, 31). For example, Manna et al. reported that RLS is significantly associated with the female gender (31). Berger et al. also reported that the incidence of RLS is approximately 10 times greater among women in the general population. No significant difference was found between the prevalence of RLS in young nulliparous women and men in Berger et al.'s study; therefore, they proposed parity as a major risk factor for RLS and suggested the role of excess estrogen in women (42). However, similar to our results, some studies have not found gender differences between patients with and without RLS (2, 4, 25, 33).

The results of our research are limited by the short duration and small number of patients enrolled in the study; therefore, multicenter clinical trials with longer durations and larger numbers of patients are needed to determine the frequency of RLS and its relationship with ESRD among patients undergoing maintenance hemodialysis.

Restless legs syndrome (RLS) is a sensorimotor disorder which causes exhaustion, sleep disturbances, daytime fatigue, and depression among most people with moderate to severe diseases. On the other hand, ESRD appears to be a risk factor for the occurrence or worsening of

RLS, and it may be associated with increased morbidity and mortality among these patients. It is reported that anemia, iron deficiency, elevated serum calcium, central nervous system abnormalities, and peripheral neuropathy secondary to uremia or the underlying cause of ESRD (such as diabetes) may predispose ESRD patients to developing RLS. According to the results of our study, a significant percentage of patients with ESRD undergoing maintenance HD have severe or very severe symptoms of RLS, and it is strongly related to increased durations of dialysis. Therefore, this disease should not be neglected or unrecognized by renal healthcare providers. Although many studies have been performed to identify the risk factors of RLS among uremic patients, the results are conflicting and, therefore, more comprehensive randomized clinical trials are needed in future.

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## Footnote

**Authors' Contribution:** Study concept and design: Seyed Seifollah Beladi-Mousavi and Seyed Mostafa Moosavian; acquisition of data: Seyed Mostafa Moosavian and Mehrian Jafarizadeh; analysis and interpretation of data: Mohammad Bahadoram; drafting of the manuscript: Seyed Mostafa Moosavian and Mohammad Bahadoram; critical revision of the manuscript for important intellectual content: Shokouh Shayanpour; statistical analysis: Mohammad Bahadoram; administrative, technical, and material support: Shokouh Shayanpour and Gholamreza Houshmand; study supervision: Seyed Seifollah Beladi-Mousavi.

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