

Examining Restless Leg Syndrome in Chronic Kidney Disease: Comprehensive Analysis

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ABSTRACT

Background: Restless Leg Syndrome (RLS) is frequently associated with Chronic Kidney Disease (CKD), often under diagnosed and inadequately treated. Hence, this study aimed to ascertain the prevalence of CKD-induced RLS, exploring associated factors, pharmacotherapy and its impact on patients' quality of life. **Materials and Methods:** An observational prospective study conducted at Dhiraj General Hospital, Vadodara, from November 2022 to March 2023 included 246 CKD patients. Screening for RLS symptoms led to further evaluation and treatment in the Neurology department. Patients were re-evaluated after one month to assess treatment outcomes. **Results:** Analysis of 246 patients revealed a 6.91% prevalence of RLS in CKD. Factors contributing to RLS included anemia, advanced CKD stages and prolonged dialysis. Female gender emerged as a CKD risk factor. Pramipexole, Syndopa and Ropirinole effectively treated RLS in CKD patients. **Conclusion:** RLS substantially diminishes the quality of life in end-stage renal disease patients. Identification and management of contributing factors hold promise for improving outcomes and quality of life in CKD patients with RLS.

Keywords: Restless Leg Syndrome, Prevalence, Chronic Kidney Disease, Willis-Ekbom Disease.

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INTRODUCTION

Restless Legs Syndrome (RLS), or Willis-Ekbom Disease, is a neurological disorder marked by degenerative changes in motor and sensory brain regions, often linked to iron deficiency. Sufferers experience leg pain and discomfort, including sensations of stiffness, itching, numbness and burning, which compel movement for relief.¹ RLS has two subgroups: primary (idiopathic) and secondary (symptomatic), with early-onset (before age 45) often indicating a genetic predisposition and late-onset (after age 45) suggesting secondary causes.² Factors like hypertension, gender, body weight and dialysis vintage influence RLS severity, with longer hemodialysis periods correlating with more severe symptoms.³ Environmental factors such as temperature changes, fatigue and stress exacerbate RLS symptoms, which can affect not just legs but also arms and other body parts.^{2,4} Levodopa is commonly perceived as effective for RLS, but many biochemical aspects, including dopamine-related anomalies, remain poorly

understood. Increased CSF levels of 3-OMD, indicating higher dopamine production, highlight the complex neurobiology of RLS.⁵ Iron deficiency is a significant factor, with a higher prevalence of RLS in individuals with iron-deficient anemia. Reduced CSF ferritin levels in RLS patients with normal peripheral iron underscore the central nervous system's role in the disorder.⁶ RLS in diabetics is linked to sympathetic activation and metabolic imbalances, contributing to symptoms alongside disrupted sleep and mood.^{7,8} Among dialysis patients, RLS is associated with increased morbidity and mortality, often attributed to dopamine and iron metabolism imbalances.⁶ Diagnosing RLS involves assessing symptoms and ruling out other conditions, often with a detailed medical history and, if needed, sleep studies.⁹ Non-drug treatments, such as lifestyle adjustments, are first-line for mild RLS, while medications like dopaminergic drugs and opioids are used for severe cases, with dose adjustments in CKD patients.¹⁰ Understanding the interplay between CKD and RLS is crucial for improving patient care.¹¹ Hepcidin may be a better marker than ferritin for iron status in RLS, particularly in CKD patients, where impaired iron transport to the brain is significant.^{6,12-14}

Restless Leg Syndrome (RLS) is common in Chronic Kidney Disease (CKD) patients but often undiagnosed due to communication challenges. This study aims to highlight the significant burden



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of RLS in CKD, securing resources for specialized services to address these unique challenges. Diagnosing and treating RLS is crucial as it can lead to anxiety and depression, worsening over time. The study will provide valuable insights into drug choices, adverse reactions and treatment efficacy, improving patient care. Additionally, understanding RLS's impact on sleep quality in CKD patients is imperative. This research is vital for enhancing RLS management and patient outcomes in CKD.

MATERIALS AND METHODS

Study Design

A prospective observational study was conducted from November 2022 to March 2023, following ethical approval from the Sumandeep Vidyapeeth Institution Ethics Committee (SVIEC/ON/Phar/BNPG21/Nov/22/20). The study focused on Chronic Kidney Disease (CKD) patients, including outpatients and those presenting to the Nephrology department at Dhiraj Hospital, SVDU.

Sample Size Calculation

Sample size was calculated using Cochran's formula. The prevalence of RLS in CKD was found to be around 20% on an average according to various study reports already published hence, using prevalence of 20% and desired precision of 0.05 we obtained the sample size.

Participants

A total of 246 CKD patients were enrolled in the study. Exclusion criteria included individuals below 18 years of age and pregnant women. Participants showing symptoms of Restless Legs Syndrome (RLS) were identified through in-person interviews and those suspected were referred to neurologists for confirmation.

Data Collection

Detailed information, including gender, age, hemodialysis history, comorbidities, medication history, family history and personal history, was documented through thorough interviews. Diagnosis of insomnia and depression was established by physicians based on comprehensive history-taking and appropriate treatment was provided.

Diagnostic Criteria for RLS

The International Restless Legs Syndrome Study Group criteria were employed for diagnosing RLS. These criteria included a strong urge to move legs accompanied by uncomfortable sensations, symptoms worsening during rest, partial relief through activity, worsening at night and the exclusion of other medical or behavioral conditions.

Psychometric Assessment

Participants were requested to complete the Center for Epidemiological Studies Depression (CESD) scale and Pittsburgh Sleep Quality Index (PSQI). PSQI assessed subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disruptions, use of hypnotic-sedative medication and daytime dysfunction. A PSQI score ≥ 5 indicated sleep disturbances, while a CESD score ≥ 16 suggested the risk of depression. Quality of life related to RLS was assessed using the RLS-QOL, with lower scores indicating poorer quality of life.

Data Analysis

Data were transcribed into Microsoft Excel and subsequently analyzed using SPSS v25. Quantitative data were presented as mean \pm standard deviation and percentage (%). Comparative statistical differences were calculated using appropriate parametric tests (e.g., odds ratio) for quantitative data and non-parametric tests for categorical data (e.g., point-biserial correlation, multivariate linear regression). Graphical representations were utilized for data visualization. A significance level of $p \leq 0.05$ was considered statistically significant.

RESULTS

Study Population

A total of 246 patients were included in the analysis, with a mean age of 48.05 ± 13.36 years. The study population was categorized into four age groups: 18 to 24, 25 to 44, 45 to 60 and greater than 60, comprising 3 (1%), 110 (45%), 80 (33%) and 53 (21%) CKD patients in each age group, respectively.

Gender Distribution

Out of the participants, 164 were males (67%) and 82 were females (33%). The mean age for male patients was 48.08 ± 12.96 years, while for female patients, it was 45.5 ± 14.14 years.

Dialysis Status

Among the study population, 101 patients (41%) were receiving dialysis as part of their CKD management.

Prevalence of RLS

Restless Legs Syndrome (RLS) was identified in 17 patients, accounting for a prevalence rate of 6.91% in the study cohort (Table 1).

Prevalence of Restless Legs Syndrome (RLS) in CKD Patients

In our comprehensive study involving 246 Chronic Kidney Disease (CKD) patients, the overall prevalence of Restless Legs Syndrome was determined to be 6.91%. When stratified by gender, the prevalence was comparable, with 6 out of 82 females (7%) and 11 out of 164 males (7%) experiencing RLS (Table 2).

Age-wise Distribution

Upon categorizing patients into three age groups (18 to 44, 45 to 64 and above 64), the prevalence of RLS varied. It was found to be 5% in the 18 to 44 age group, 10% in the 45 to 64 age group and 3% in those aged above 64.

Socio-Economic Status

Analyzing socio-economic status revealed a slightly higher prevalence of RLS in the lower class (7%) compared to the middle class (6%).

Social History

Patients with a history of smoking exhibited a higher prevalence of RLS at 8%, while the prevalence among alcoholics and tobacco chewers was 5% and 6%, respectively.

Co-morbidities

Among patients with associated medical conditions, the prevalence of RLS was 8% in those with type II Diabetes mellitus, 11% in hypertensive patients and 7.6% in individuals with anemia.

CKD Staging

Significantly, the prevalence of RLS was notably higher in CKD Stage V patients, reaching 16%. CKD Stage IV patients showed a prevalence of 4%, while Stages I, II and III had prevalence rates of 7%, 3% and 2%, respectively.

Our logistic regression analysis revealed key insights into the odds of Restless Legs Syndrome (RLS) across demographic and lifestyle factors. Patients aged 45-60 had 0.54 times higher odds and those above 60 had 1.95 times higher odds of RLS compared to those under 44. Females had 1.09 times higher odds of RLS than males. Lower socio-economic status increased the odds by 1.26 times. Lifestyle factors also played a role: alcohol consumption increased the odds by 1.99 times, smoking by 1.18 times and tobacco chewing showed 0.89 times higher odds. These findings highlight the complex interplay of age, gender, socio-economic status and lifestyle in RLS risk. Our analysis identified significant associations between Fasting Blood Sugar (FBS) levels, HbA1c levels and the frequency and duration of dialysis with RLS ($p < 0.05$), but not with Hemoglobin (Hb) or serum ferritin levels ($p > 0.05$). This underscores the importance of glycaemic control and dialysis parameters in RLS, suggesting targeted intervention opportunities. Pharmacologically, Pramipexole was the primary treatment for 9 out of 17 RLS patients, with Syndopa and Ropinirole each used in 4 patients. This highlights Pramipexole's prevalence and potential efficacy in managing RLS symptoms in CKD patients. Quality of life assessments using standardized questionnaires indicated that 82% of RLS patients were at risk of depression (CESD), 76% had impaired Quality of Life (RLS-QOL) and 100% had Poor Sleep Quality (PSQI). These findings emphasize RLS's significant impact on psychological well-being, overall quality of life and sleep in CKD patients, highlighting the

Table 1: Prevalence of RLS Patients in Chronic Kidney Disease Patients.

Study Variables	Groups	Patients with RLS/Total CKD Patients in the group	Prevalence	p-value
Age	18 -24	0/3	-	0.06167
	25-44	6/110	5.6%	
	45-60	3/80	3.8%	
	>60	8/53	15.6%	
Gender	Male	11/164	7%	0.86
	Female	6/82	7%	
Socio Economic Status	Middle Class Low	4/68	6%	0.6943
	Class	13/178	7%	
Social History	Alcoholic	5/109	5%	-
	Smoker	7/92	8%	
	Tobacco	5/78	6%	
	Chewer			
Medical History	Diabetes	8/99	8%	-
	Hypertension	13/111	12%	
	Anaemia	17/242	7.02%	
CKD Stage	I	1/14	7%	0.00598
	II III	1/37	3%	
	IV	/63	2%	
	V	/57	4%	
		12/75	16%	

need for comprehensive management strategies. The severity of RLS was assessed using the IRLS rating scale, showing that 47% had moderate RLS, 24% had severe RLS, 18% had mild RLS and 12% had very severe RLS (Table 3). This spectrum of severity underscores the importance of tailoring treatment to individual symptom levels. Our univariate regression analysis examined the relationship between the severity of Restless Legs Syndrome (RLS) and various outcome measures, including PSQI, CESD and RLS-QOL scores. The analysis revealed statistically significant relationships between IRLS scores before treatment and all three outcome measures ($p < 0.05$). These findings underscore the interconnectedness of RLS severity with sleep quality, depressive symptoms and overall quality of life, emphasizing the need for

a comprehensive, multidimensional approach to manage RLS in chronic kidney disease patients.

In our analysis, both Univariate and Multivariate Regression were employed on the IRLS Before treatment scores to elucidate the variability in these scores attributed to various variables. The Univariate analysis revealed statistically significant relationships between being a smoker, FBS Level, Dialysis and Hypertension with RLS Before treatment Scores (p value <0.05). However, when these eligible variables were considered in a multivariate model, no substantial modification was observed in the explanatory model. Surprisingly, none of the variables emerged as significant contributors to the multivariate explanatory model, suggesting

Table 2: Demographic representation with Odds Ratio.

Factors	Patients with RLS/Total Patients in the Group	Odds Ratio (95% CI)	p value
Age	25-44 (6/110)	-	-
	45-60 (3/80)	0.54 [0.061, 4.801]	0.291
	>60 (8/53)	1.95 [0.652, 5.810]	0.116
Gender	Male (11/164)	-	-
	Female (6/82)	1.09 [0.391, 3.082]	0.429
Socio Economic Status	Middle Class (4/68)	-	-
	Lower Class (13/178)	1.26 [0.396, 4.010]	0.347
Alcoholic	No (12/137)	-	-
	Yes (5/109)	1.99 [0.681, 5.852]	0.103
Smoker	No (10/154)	-	-
	Yes (7/92)	1.18 [0.435, 3.231]	0.369
Tobacco Chewer	No (12/168)	-	-
	Yes (5/78)	0.89 [0.302, 2.621]	0.416

Table 3: Univariate and Multivariate regression of RLS-Before Treatment scores.

	Univariate regression for RLS-Before Treatment			Multivariate Regression for RLS-Before Treatment R2=28.3		
	Coefficient	SE	p value	Coefficient	SE	p value
Gender	5.28	3.72	0.175			
Age	-0.153	0.146	0.312			
Socio Economic Status	2.5	4.41	0.579			
Alcoholic	1.43	4.13	0.734			
Smoker	3.12	3.76	0.042	0.58	0.87	0.66
Tobacco chewer	5.116	3.93	0.213			
Diabetic	-2.29	3.74	0.549			
Hb Level	1.59	1.36	0.26			
Serum Ferritin	0.033	0.03	0.319			
FBS Level	-0.086	0.031	0.014	-0.26	1.10	-0.24
Dialysis	0.738	4.59	0.013	1.44	2.92	0.49
Hypertension	2.81	4.09	0.05	2.11	3.97	0.56

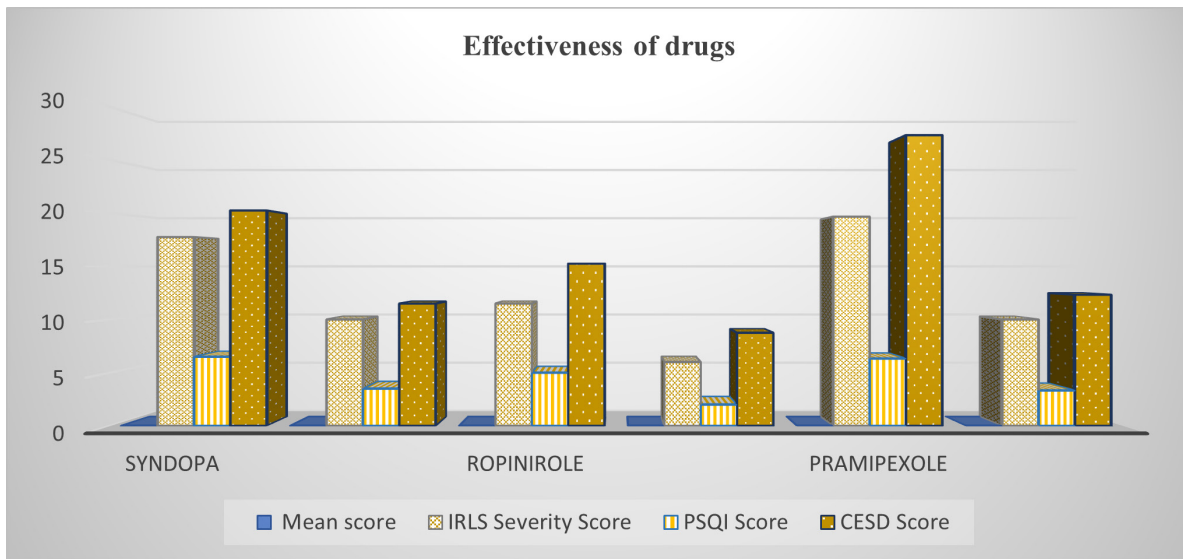


Figure 1: Effectiveness of Drugs in RLS Patients.

that the interplay of these factors may not collectively account for the observed variability in the severity of Restless Legs Syndrome before treatment.

In our study, we compared the effectiveness of three drugs—Syndopa, Ropinirole and Pramipexole—based on IRLS Severity Score, PSQI Score, CESD Score and RLS QOL Score (Figure 1). Mean differences were analyzed, revealing that patients treated with Pramipexole exhibited the highest differences in IRLS, CSED and RLS QOL scores, indicating its superior effectiveness in alleviating Restless Legs Syndrome symptoms. However, for PSQI, all three drugs demonstrated comparable efficacy, with no significant differences in the mean scores observed among them. This suggests that, while Pramipexole stands out as the most effective for certain aspects of RLS management, the three drugs perform equally well in addressing sleep quality issues.

DISCUSSION

Our study highlights the prevalence of Restless Legs Syndrome (RLS) in Chronic Kidney Disease (CKD) patients, noting significant variations across different CKD stages. We observed a 6.9% prevalence of RLS in CKD patients, increasing to 16% in end-stage CKD patients undergoing hemodialysis. Global literature reveals a wide range of RLS prevalence in dialysis patients, from 6.6% to 70%. Our findings showed a lower prevalence compared to Western studies (20% to 57.4%), while a study in China reported a higher prevalence of 70% in hemodialysis patients, indicating regional differences. An Indian study found 10.3% prevalence, reflecting diverse rates across populations. A 2018 review emphasized elevated RLS rates of 15% to 30% in dialysis patients, exceeding the general population's prevalence of 5% to 10%. These insights suggest the need for further research into regional and population-specific factors affecting RLS prevalence in CKD.¹⁵⁻¹⁷ Our study provides

insights into the prevalence of Restless Legs Syndrome (RLS) among male and female Chronic Kidney Disease (CKD) patients, revealing an equal prevalence of 7% in both genders. However, statistical analysis indicated that females had a higher likelihood of developing RLS. This discrepancy prompts a closer look at gender-specific factors influencing RLS in CKD patients. A 2022 study, adjusting for confounding factors, reported significantly greater odds of RLS in women (odds ratio 2.8 [95% confidence intervals 1.5-5.2]). These findings highlight the complexity of the relationship between gender and RLS in CKD, suggesting further investigation into gender-specific risk factors are needed.^{18,19} Our study found a significant association between Restless Legs Syndrome (RLS) and anemia in Chronic Kidney Disease (CKD) patients, with all 17 RLS-affected individuals also presenting with anemia. The prevalence of RLS among anemic CKD patients was 7.6%, aligning with our study results. However, other studies reported higher RLS prevalence in anemic CKD patients. For example, a 2013 study found a 31% RLS prevalence in CKD patients with Iron-Deficiency Anemia (IDA) compared to 7% without IDA. Statistical analysis in our study did not find a significant association between hemoglobin levels, serum ferritin levels and RLS, contradicting studies that suggest a prominent role of iron deficiency in RLS development. Diagnosing iron status in CKD is challenging due to the acute phase reactant role of ferritin and the inflammatory state characteristic of CKD, which can lead to normal or high ferritin levels despite underlying iron deficiency.^{20,21}

Our study determined the prevalence of Restless Legs Syndrome (RLS) in Chronic Kidney Disease (CKD) patients with type II diabetes to be 8%. Statistical analysis revealed an association between RLS and Fasting Blood Sugar (FBS) levels, as well as HbA1c levels. Univariate regression analysis indicated a significant relationship between fasting blood glucose and RLS severity, with higher RLS severity in individuals with elevated FBS

levels. However, no significant relationship was found between RLS severity and HbA1c levels. A study supporting our findings emphasized polyneuropathy as a primary risk factor for RLS in diabetics but noted that RLS occurrence in type 2 diabetics cannot be solely attributed to polyneuropathy, suggesting the need for further research. These results highlight the complex interplay between diabetes-related parameters and RLS in CKD patients, prompting further investigation into underlying mechanisms and potential therapies.^{22,23}

In our study, the prevalence of Restless Legs Syndrome (RLS) among Chronic Kidney Disease (CKD) patients with a history of alcohol intake, smoking and tobacco chewing was 5%, 8% and 6%, respectively. We found a significant association between RLS severity and a history of smoking. This aligns with research showing an elevated risk of RLS among daily alcohol consumers (OR=4.716, $p=0.022$) and the link between RLS, alcohol use and smoking. A meta-analysis identified 20 sequence variations at 19 loci associated with RLS, highlighting the genetic component. These results underscore the multifactorial nature of RLS, involving lifestyle factors, genetics and interactions, necessitating comprehensive investigations for a holistic understanding in CKD patients.^{22,24,25}

Our study identified hypertension as a significant comorbid condition among Chronic Kidney Disease (CKD) patients, surpassing diabetes. The prevalence of Restless Legs Syndrome (RLS) among CKD patients with hypertension was 12%, higher than in the general population. A 2018 study suggested a potential link between antihypertensive drugs and RLS. Various studies have explored hypertension as a risk factor for RLS, though findings have varied. The interplay between hypertension, antihypertensive medications and RLS requires further investigation.²⁶ Our study also highlighted the association between dialysis frequency and duration and an increased risk of RLS in CKD patients. This contrasts with some earlier studies that found no substantial connection. We propose that anemia, regardless of iron reserves, may significantly contribute to RLS development in dialysis patients. Reduced erythropoietin production due to impaired renal function affects erythropoiesis and iron transport to the CNS. Our findings align with previous research on hemodialysis patients, showing a link between RLS and reduced hemoglobin levels. A meta-analysis by Mao *et al.* supported these findings, noting significantly lower hemoglobin and iron levels in dialysis patients with RLS compared to those without RLS globally.^{12,27}

Our study highlights the multifaceted impact of Restless Legs Syndrome (RLS) on Chronic Kidney Disease (CKD) patients, showing significant associations with sleep disturbances, depression and impaired quality of life. The Pittsburgh Sleep Quality Index (PSQI) revealed uniformly poor sleep among all 17 RLS patients, with 15 exhibiting excessive daytime sleepiness. This aligns with a 2017 study that found increased sleep disturbances

and depression in CKD patients with RLS. Quality of Life (QoL) was notably worse in uremic RLS patients, with a 25% decline in QoL scores compared to idiopathic RLS patients. Additionally, 20% of hemodialysis patients reported premature treatment cessation due to RLS symptoms. The interplay of RLS with sleep issues, leg twitching and insomnia presents complex challenges for CKD patients, with gender disparities amplifying the impact on women.^{28,29}

Our study treated Restless Legs Syndrome (RLS) in patients using Pramipexole 0.125 mg, Ropinirole 0.25 mg and Syndopa 110 mg, but did not investigate dose variations due to uniform drug administration likely influenced by concurrent anemia. All 17 RLS patients received T. Supradyn for anemia and two with severe depression received T. Protiaden (Doxepin) 25 mg. Pramipexole was the most effective, improving symptoms and quality of life within a month, aligning with studies showing Ropinirole's benefits for RLS symptoms and sleep quality. Our review highlights non-pharmacological therapies for mild to moderate RLS, including transcranial magnetic stimulation, physical activity, compression gear, counter-strain manipulation, infrared therapy, acupuncture, vibration pads, cryotherapy, yoga, and compression garments. Future research should consider potential placebo effects in RLS management.³⁰

The lower prevalence of Restless Legs Syndrome (RLS) in our study may be due to the smaller proportion of female Chronic Kidney Disease (CKD) patients, as RLS is more common in females. This highlights the limitation of our small sample size, especially in the RLS subset. The small sample size and limited laboratory data hinder identifying etiological factors like parathyroid hormone and estrogen levels and assessing pharmacotherapy efficacy. The short study duration also restricted the investigation of treatment side effects and adverse reactions. Despite these limitations, our study provides valuable insights into RLS prevalence and management in CKD, underscoring the need for larger sample sizes and longer study durations in future research.

CONCLUSION

In summary, this research emphasizes how Restless Leg Syndrome (RLS) affects the well-being of people with Chronic Kidney Disease (CKD), especially as CKD progresses. It's important to identify the factors that increase the risk of RLS. Using appropriate treatment options can help improve the overall health and well-being of people dealing with RLS and CKD.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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