The Role of Anemia to Restless Legs Syndrome in Regular Hemodialysis Patients in Haji Adam Malik Medan General Hospital

Rasyidah Hasan Harahap[1], Riri Andri Muzasti[2*]
[1]*Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital, Medan, Indonesia*
[2]*Division Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital, Medan, Indonesia*
Corresponding author: Riri Andri Muzasti, Division Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital, Medan, Indonesia
Jl. Bunga Lau No.17, Medan, Indonesia, Phone/facsimile:+62-61-8365742.

Keywords: anemia, restless legs syndrome, hemodialysis

Abstract: **Background:** Restless Syndrome (RLS) has a higher prevalence in hemodialysis (HD) patients compared to the general population. Anemia as a cause of the high prevalence of RLS in HD is still unclear. **Method:** This is a cross-sectional study conducted in October 2017 evaluated 106 regular HD patients in Haji Adam Malik Medan General Hospital who had fulfilled inclusion and exclusion criteria. RLS diagnoses and severity was done in face to face interview according to the International Restless Legs Syndrome Study Group. Biochemical characteristics were measured. Bivariate and multivariate analysis was performed. **Results:** Of the 106 patients who took part in this study, RLS was found in 32 patients (30.2%). Hb levels in regular hemodialysis patients with RLS have a lower mean than patients without RLS. In the multivariate analysis using multinomial regression it was found that age and TIBC levels were associated with RLS and Hb as a protection factor for RLS OR 0.697 95% CI 0.496 ± 0.98. **Conclusion:** Anemia is one of the factors that influence the occurrence of RLS in addition to age being a matter that must be considered in the prevention and management of RLS in hemodialysis patients.

1 INTRODUCTION

Restless Legs Syndrome (RLS) is one of the most common sleep disorders in dialysis patients with a prevalence reaching 20% in patients with Chronic Kidney Disease (CKD) (Scherer JS, et al., 2017). Some literature shows an association between RLS and quality of life and mortality of patients with HD (*what HD stand for?)* (Neves, et al., 2017). Patients with HD who have RLS, have a higher mortality rate compared to patients without RLS (32.3% vs. 14.5%; p <0.04) with Hazard Ratio 1.39; 95% CI 1.08-1.79) (Scherer JS, et al., 2017).

Decreasing HD prevalence of RLS in patients who have received kidney transplantation (4% vs. 11%; p <0.001) illustrates that kidney disease itself plays a role in the occurrence of RLS (Scherer JS, et al., 2017).

It was already known that one of the complications of CKD is anemia (Suwitra, 2014). In dialysis patients, anemia is considered to be the main cause of RLS regardless of available iron reserves (Menezes, et al., 2018). However, several studies are not in line with this finding (Kim, et al., 2008).

The pathophysiology of anemia with the occurrence of RLS in regular hemodialysis patients is still unclear. Therefore, we were interested in knowing the relationship of anemia with RLS in regular HD patients. This is important to be used as prevention and management of RLS in regular hemodialysis patients. *The aim of the study…..*

Harahap, R. and Muzasti, R.
The Role of Anemia to Restless Legs Syndrome in Regular Hemodialysis Patients in Haji Adam Malik Medan General Hospital.
DOI: 10.5220/0009863702210226
In *Proceedings of the 2nd International Conference on Tropical Medicine and Infectious Disease (ICTROMI 2019)*, pages 221-226
ISBN: 978-989-758-469-5

2 METHODS

2.1 Data Collection

This is an observational analytic study with cross-sectional study design. Aim of this study is to ascertain the relationship between anemia and RLS in regular hemodialysis patients. The study was conducted in October 2017 at the Adam Malik Haji Hospital in Medan.

All patients undergoing hemodialysis therapy at Adam Malik Haji Hospital in Medan and willing to take part in the study and fulfill the inclusion and exclusion criteria were included. Inclusion/exclusion criteria: age 18 years old or older, patients who have stably undergone hemodialysis more than 3 months, not suffering or being treated from infection, malignancy or drug / alcohol abuse, neurological disorders, heart, lung and heart disease and have complete data *(what about blood transfusion? Mostly HD with blood transfusion)*

Data collected from primary data and secondary data. Primary data is data obtained from interviews for patient data and filling out questionnaires. Secondary data obtained from medical records in the form of laboratory results. (*mention same result of laboratory use for this research).* Before data collection from the sample is carried out, samples that are in accordance with the inclusion and exclusion criteria will be given a research explanation and informed consent if agreed, the hemodialysis patients can be used as research samples. In this study, there were 106 patients who participated in the study *(How to calculate this 106 sample, How to choose the sample, for example, consecutive sampling or convenience sampling the author must write it)*

Patients are diagnosed with RLS if they fulfill all criteria by the International Restless Legs Syndrome Study Group (IRLSSG). Patients who met the criteria continued with interviews to determine the degree of RLS based on the International RLS Severity Scale (IRLS). *What kind of research instrument used in this research, what about ethical clearance? Is valid and reliable? The author must mention it clearly)*

2.2 Statistical Analysis

All data were analyzed with statistical software SPSS 22.0 using univariate, bivariate and multivariate analysis with 95% confidence interval. Bivariate analysis was carried out using chi-square to compare patients with and without RLS. Pearson correlation examined the relationship between single variables. Multinomial logistic regression was also performed to investigate factors associated with RLS, adjusting for covariates *(more explanation about using chi-square, person correlation, and multivariate, what data using for each statistical analytic).*

3 RESULTS

Table 1. Of the 106 patients who attended the study, all patients underwent HD 2 times a month. Men have a higher prevalence than a woman (66% vs 34%). The Mean age of regular HD patients was 48.4 ± 13.29 with HD duration mean 24.2 ± 12.45. Mean of hemoglobin level is 9.15 ± 1.47, SI 66.9 ± 33.7, TIBC 191.8 ± 58.8, transferrin saturation 37.3 ± 19.61, ferritin levels 983.8 ± 932.86. The mean of mineral level calcium is 8.13 ± 0.96, and phosphate level is 5.6 ± 2.13. Of 32 patients (30.2%) with respect to the severity of RLS, 4 patients classified as mild (12.5%), 15 patients had moderate (46.9%), 9 had severe (28.1%) and 4 patients had very severe (12.5%). 74 patients have no symptom of RLS. *(explanation the table used to after the table, not before the table show).*

Table 1: Baseline characteristic regular hemodialysis patients in Haji Adam Malik General Hospital.

Variable	n (%); Mean ± SD
Gender	
Men	70 (66%)
Women	36 (34%)
Age (years)	48,4 ± 13,29
HD (month)	24,2 ± 12,45
Hb (gr/dL)	9,15 ± 1,47
SI (µg/dL)	66,9 ± 33,7
TIBC (µg/dL)	191,8 ± 58,8
Ferritin (µg/dL)	983,8 ± 932,86
ST (%)	37,3 ± 19,61
Ca (mg/dL)	8,13 ± 0,96
P (mg/dL)	5,6 ± 2,13
RLS	
RLS	32 (30,2)
without RLS	74 (69,8)
RLS severity	
Mild	4 (12,5)
Moderate	15 (46,9)
Severe	9 (28,1)
Very severe	4 (12,5)

Table 2: Characteristic of patients according to restless legs syndrome presence or absence

	Tanpa RLS (n = 74)	RLS (n = 32)	P value
Gender			0,377
Men	51 (68,9)	19 (59,4)	
Women	23 (31,1)	13 (40,6)	
Age (years)	44,4 ± 14,32	50,1 ± 12,55	0,044*
HD (month)	25,2 ± 12,76	23,8 ± 12,08	0,604
Hb (gr/dL)	9,5 ± 1,42	9,0 ± 1,47	0,102
<10	56	21	0,287
>10	18	11	
SI (µg/dL)	68,4 ± 39,43	66,3 ± 31,1	0,764
TIBC (µg/dL)	178,8 ± 52,35	197,4 ± 60,89	0,135
Ferritin (µg/dL)	893,3 ± 952,94	1193 ± 862,75	0,129
ST (%)	38,3 ± 21,41	36,8 ± 18,92	0,714
Ca (mg/dL)	8,3 ± 0,84	8,1 ± 1,01	0,251
P (mg/dL)	5,7 ± 2,24	5,5 ± 2,09	0,675

We found age was significantly associated with the incidence (prevalence) of RLS with p = 0.044, where the mean age at RLS (50.1 ± 12.55) was older than without RLS (44.4 ± 14.32). In this study long HD was not significantly different between RLS and without RLS. Anemia profile showed lower Hb levels (Hb averaged 9,0 ± 1.47 vs. 9.5 ± 1.42), lower SI and TSAT ?? levels and higher of TIBC and ferritin level in RLS than without RLS. There was no statistically significant difference in calcium and phosphate levels in this study between RLS and without RLS.

Table 3. Variables that have a value of p <0.25 are included in the multivariate analysis. From the results of multivariate analysis, it was found that RLS was influenced by levels of TIBC, Hb and age.

Table 3: Multinomial logistic regression predicting the presence/ absence of restless legs syndrome

Variable	OR	P Value	95% CI
TIBC	1,010	0,020	1,002 ± 1,019
Hb	0,697	0,038	0,496 ± 0,981
Age	1,040	0,025	1,005 ± 1,076

4 DISCUSSION

In this study, the prevalence of RLS in regular HD patients was 30.2%. This prevalence is in accordance with previous research reports using IRLSSG where the prevalence of RLS in dialysis patients was around 20% -62% (Saraji, et al., 2017). This was also in line with previous studies by Marta et al (12-25%), Scherer JS et al (10-20%) (Scherer JS, et al., 2017), Guo et al (20-30%) (Guo, et al., 2017), Rohani et al (37.4%) (Rohani, et al., 2015). Higher incidence of RLS in HD patients is also supported by data from various other studies such as in Sao Paolo on 101 dialysis patients found 29 patients (28.7%) with RLS (Kim, et al., 2008), the study of Zamani et al in Mashad Iran found RLS prevalence reached 31.7% (Saraji, et al., 2017), and Al-Jahdali et al with RLS prevalence of 50.22% (Higuchi, et al., 2015). The prevalence that is quite varied in various regions can be caused by differences in race, culture, socio-economic status, or available health facilities (Takaki, et al., 2003).

In this study, there was no relationship between sex and RLS. In this study, RLS was more common in men than in women as in the study by Takaki et al (Takaki, et al., 2003). Previous studies by Kim et al also showed the same thing (Kim, et al., 2008). Gender does not affect the occurrence of RLS in dialysis patients (Kim, et al., 2008). Differences from previous studies may be explained by differences in proportions in each study (Saraji, et al., 2017).

The existence of a relationship that was statistically significant between age and the incidence of RLS was found in this study. The average age of patients with RLS is higher than the group without RLS. Although different from the study by Jeong Min Kim et al who found age did not affect the occurrence of RLS (Kim, et al., 2008). Secondary RLS usually occurs in patients over 40 years of age and is associated with various neurological disorders (Guo, et al., 2017). The previous study has concluded that the prevalence and severity of RLS levels that increase with age suggest that the neurodegeneration process plays an important role in the occurrence of RLS (Kim, et al., 2008) (Guo, et al., 2017).

This is in line with the study of Saraji et al on dialysis patients who showed an increase in the prevalence of RLS with age (p = 0.002) (Saraji, et al., 2017) and a study by Ki et al. Which showed a tendency of RLS with age (Ki, et al., 2010).

In a previous study by Kim et al and Araujo et al, The duration of dialysis did not affect the occurrence of RLS in dialysis patients (Kim, et al., 2008) (Araujo, et al., 2010). This study also showed no association between the duration of hemodialysis and the occurrence of RLS. The duration of dialysis is not proven to improve or worsen RLS complaints.

Significant relationship between Hb level and RLS (OR 0.697 0.496 ± 0.981, p = 0.038) can be seen in this study. This is in accordance with the study by Takaki et al (OR 0.741 0.551-0.997, p = 0.0475) (Takaki, et al., 2003). Precil et al. Also proved that there was a relationship between Hb levels <9.8 g / dL and the occurrence of RLS (OR 1.84 1.03-2.79, p = 0.040) (Neves, et al., 2017). Similarly, Araujo et al. proved the association of RLS in dialysis patients and decreased Hb (p <0.005) (Araujo, et al., 2010). Based on the results of a Meta-analysis study of 23 previous studies Mao et al found lower Hb levels than patients without RLS (Menezes, et al., 2018). Along with decreased kidney function, there will be a decrease in the production of erythropoietin which is the main cause of anemia in kidney disease (Babitt & Lin, 2012). Decreasing erythropoietin will cause a decrease in erythropoiesis where in a way that is still not fully (Kim, et al., 2008)known, reduce iron transport to the central nervous system (CNS) and medulla (Menezes, et al., 2018). Several recent studies have

shown that anemia, regardless of the iron content, is a major cause of RLS (Menezes, et al., 2018). However, several other studies are not in line with this finding (Kim, et al., 2008).

Iron deficiency anemia is known to be one of the risk factors for RLS (Kim, et al., 2008). Iron is needed for recycling dopamine in the nervous system and is the main cofactor for the regulation of dopamine synthesis (eg Tyrosine hydroxylase) (Scherer JS, et al., 2017). However, this is not very clear in dialysis patients because of the use of iron supplements in this population (Scherer JS, et al., 2017). Iron deficiency in dialysis patients defined by the Japanese Society for Dialysis Therapy (JSDT) is serum ferritin levels <100ng / dL and TSAT <20% (Higuchi, et al., 2015) (Yamamoto, et al., 2015). In patients who meet the criteria will receive iron supplementation both oral and intravenous (Kim, et al., 2008). This, of course, can obscure the relationship between serum iron and serum ferritin and TSAT with RLS in this study (Kim, et al., 2008). In this study, no significant association was found between serum iron and TSAT with RLS in line with Terumi et al (Higuchi, et al., 2015). In addition, in some circumstances, RLS can be found even though the serum iron value is normal (Wijemanne & Ondo, 2017). This is because peripheral iron values cannot describe the low iron in the brain (Wijemanne & Ondo, 2017). Therefore a neuropathological examination such as imaging (MRI) and cerebrospinal fluid examination is needed (Wijemanne & Ondo, 2017).

In this study, there was no association between serum ferritin and TSAT in RLS patients and without RLS. These results are in line with the study by Terumi et al.who did not find any association between serum ferritin and RLS (Higuchi, et al., 2015). This is in contrast to the study of Guo et al. who found an association of the degree of RLS with ferritin values (Guo, et al., 2017). Mean serum ferritin which tended to increase and lower TSAT in RLS patients than patients without RLS showed that ferritin values could not be used as deposit predictors iron and can better describe iron status in iron deficiency (Menezes, et al., 2018) (Saraji, et al., 2017). In addition, iron supplementation also obscures the relationship between them (Saraji, et al., 2017). Ferritin levels can also be affected by other factors such as inflammation and oxidative stress (Higuchi, et al., 2015) (Babitt & Lin, 2012). In this study, we have excluded patients in treatment, infections, malignancies, and other factors that cause inflammation based on interviews and physical examinations. But this cannot rule out other inflammatory factors. Therefore, in subsequent studies, it is recommended to examine inflammatory markers as monitoring.

From the bivariate analysis, we found a significant relationship between the increase in TIBC values and the occurrence of RLS. This is something new in this study. Previous studies were more likely to analyze hemoglobin, serum iron and ferritin to see the iron status in the body (KDIGO, 2012). TIBC examinations to see as iron status analysis are rare. Serum iron and TIBC comparison values to see TSAT is more commonly found and show insignificant results as in a study by Precil et al and Terumi et al (Neves, et al., 2017) (Rohani, et al., 2015) (Neves, et al., 2017) (Higuchi, et al., 2015). Serum ferritin values that can be influenced by factors such as inflammation also have a non-significant relationship in RLS in this study. Therefore, TIBC can be considered a marker for assessing iron status in dialysis patients.

The relationship between phosphate levels to RLS cannot be proven in this study. The calcium-phosphate balance associated with RLS is controversial (Saraji, et al., 2017). Study by Roberto et al found an improvement in RLS complaints and a decrease in phosphate levels after parathyroidectomy (Menezes, et al., 2018), was not in line with other studies by Filho et al., La manna et al, Terumi et al, and Saraji et al. who also found no association between phosphate and calcium levels with RLS (Higuchi, et al., 2015) (Saraji, et al., 2017).

Of the 106 patients who took part in the study, 32 patients (30.2%) had RLS with mild severity of 4 patients (12.5%), moderate 15 patients (46.9%), severe 9 patients (28,1%) and very severe 4 patients (12.5%). Patients who did not experience RLS were 74 patients (69.8%). Based on the results of statistical tests by comparing age, Hb levels and TIBC values in light-to-moderate and severely severe RLS patients no significant differences were found between the two groups. The number of samples and proportions may be the factors that influence the results of the study. In addition, other factors such as drug use and iron supplementation can be biased.

This research is a cross-sectional study. Therefore, the cause of the relationship cannot be determined. There is limited research that has the potential to be biased because of the limited sample and data obtained from interviews such as medical history, drug use (HD patients tend to consume more drugs including benzodiazepines, gabapentin, tricyclics) cannot play a role in RLS. Further

research is needed to approach risk factors and pathophysiology in RLS.

5 CONCLUSION

In this study, the prevalence of RLS in regular HD patients is 30.2%. We found that RLS status was influenced by Hb, TIBC, and age. RLS is often found in HD patients but is still often undiagnosed and untreated. RLS creates a disruption in quality of life and increases mortality risk, therefore screening for RLS is best done at health facilities that provide services for renal replacement therapy especially hemodialysis. The need for education about RLS for HD patients to make it more routine for screening (anemia) and prevention, especially for patients who are older.

Pathophysiology of RLS is still unknown and multifactorial, with the availability of complete data and larger samples it is expected that other factors related to RLS can be identified. In accordance with the results of the study where low Hb levels and high TIBC are significant risk factors, it is recommended to correct anemia as prevention and management of RLS.

REFERENCES

Araujo, S. et al., 2010. Restless legs syndrome in end-stage renal disease: clinical characteristic and associated comorbidities. *J sleep,* 11(8), pp. 789-790.

Babitt, J. & Lin, H., 2012. Mechanism of anemia in CKD. *JAm Soc Nephrol,* Volume 23, pp. 1631-1634.

Guo, S. et al., 2017. Restless legs syndrome: from pathophysiology to clinical diagnosis and management. *Front Aging Neurosci,* 171(9), pp. 1-14.

Higuchi, T. et al., 2015. Association of Restless Legs Patient syndrome with oxidative stress and inflammation. *Jsleep,* Volume 16, pp. 941-948.

KDIGO, 2012. KDIGO Clinical practice guideline for anemia in chronoc kidney disease. *Kidney Int Suppl,* Volume 2, pp. 2279-2335.

Ki, K. et al., 2010. Prevalence, comorbidities and risk factor of restlesslegs syndrome in the Korean elderly population-result from the korean longitudinal study on health and aging. *J Sleep res,* Volume 26, pp. 1976-1983.

Kim, J. et al., 2008. Restless legs syndrome in patient on hemodialysis. *J Clin Neurol,* Volume 4, pp. 153-157.

Menezes, A. F. d. et al., 2018. Restless legs syndrome in dialysis patients: does dialysis modality influence its occurence and severity. *Int J Neph,* Volume 2018, pp. 1-6.

Neves, P. et al., 2017. Effect of mineral and bone metabolism on restless legs syndrome in hemodialysis patients. *J slsci,* 13(1), pp. 89-94.

Rohani, M., Aghaei, M., Jenabi, A. & Yazdanfar, S., 2015. Restless legs syndrome in hemodialysis patients in Iran. *Neurol Sci,* 36(5), pp. 723-727.

Saraji, N., Hami, M., B, R. & Mojahedi, M., 2017. Restless legs syndrome in chronic hemodialysis patients in Mashad hemodialysis centers. *J renal inj prev,* 6(2), pp. 137-141.

Scherer JS, Combs SA & Brennan F, 2017. Sleep disorders, Restless Legs Syndrome and Uremic Pruritus: Diagnosis and Treatment of common symptoms in dialysis patients. *AmJ Kidney Dis,* 69(1), pp. 117-128.

Suwitra, K., 2014. *Penyakit Ginjal Kronik.* 6 ed. Jakarta: InternaPublishing.

Takaki, J. et al., 2003. Clinical and physilogical aspects of restless legs syndrome in uremic patients on hemodialysis. *AmJ Kidney Dis,* Volume 41, pp. 833-839.

Wijemanne, S. & Ondo, W., 2017. Restless Leg Syndrome: clinical features, diagnosis and practical approach to management. *Pract Neurol,* Volume 17, pp. 444-452.

Yamamoto, H. et al., 2015. Japanese study for dialysis therapy: Guidelines for renal anemia in chronic kidney disease. *Renal replacement therapy,* 3(36), pp. 1-46.