[*Lestari * et al., 6(4): April, 2019*]

ISSN: 234-5197
Impact Factor: 3.765

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

# RELATIONSHIP BETWEEN INTERLEUKIN-6 LEVELS AND PRURITIC EVENTS IN PATIENTS WITH CHRONIC KIDNEY DISEASE UNDERGOING REGULAR HEMODIALYSIS

**Dewi Fuji Lestari*[1], Riri A. Muzasti[2] & Syafrizal Nasution[2]**

[1]Resident Department of Internal Medicine, Faculty of Medicine, University of North Sumatra
[2]Nephrology Division Department of Internal Medicine, Faculty of Medicine, University of North Sumatra

**DOI: 10.5281/zenodo.2634694**

**Keywords:** Interleukin-6, Pruritus , CKD.

## Abstract

**Introduction**: Patients with chronic kidney disease (CKD) who undergo hemodialysis often have several complaints and pruritus is estimated to occur in 20% - 90% of these patients. Inflammation is thought to play an important role in pruritus in hemodialysis patients. Among a number of pro-inflammatory cytokines, research shows that IL-6 is the central regulator of the inflammatory process, and is found in dermal nerve fibers.

**Method**: This is an analytical study with cross-sectional design to determine the relationship between IL-6 levels and the incidence of pruritus in CKD patients undergoing regular hemodialysis. Patients were asked to fill out the Pauli-Magnus questionnaire and a serum level of IL-6 laboratory test was then conducted. After the data was collected, data processing and analysis were conducted.

**Results**: Of 100 patients, it was found that IL-6 levels were statistically associated with the incidence of pruritus (0.001).

**Conclusion:** From this study it can be concluded that there was a relationship between IL-6 levels and the incidence of pruritus in CKD patients undergoing regular hemodialysis.

## Introduction

Chronic kidney disease (CKD) is a global and national health problem due to its incidence tends to increase, it also has a poor prognosis, and requires high costs. The most common modality of treatment is hemodialysis. The 2014 IRR report also showed that hemodialysis accounted for 82% of renal replacement therapy (RCT) services, of which 249 renal units reports, 30.554 patients were actively undergoing dialysis in 2015, most of them were CKD patients.[1, 2]

Patients undergoing hemodialysis often have several complaints where pruritus is estimated to occur in 20% - 90% of dialysis patients.[3,4] In a large-scale study of the Dialysis Outcomes and Practice Patterns Study (DOPPS) I and DOPPS II, it was reported that > 40% of patients undergoing hemodialysis had chronic pruritus.[5] Although pruritus can be temporary for several months, these symptoms more often last more than 1 year.[6]

Inflammation is thought to play an important role in pruritus in hemodialysis patients. Among a number of pro-inflammatory cytokines, research shows that IL-6 is the central regulator of the inflammatory process, and is found in dermal nerve fibers.[7] Research conducted by Kimmel et al also stated that serum IL-6 levels were significantly increased in pruritus patients compared with patients without pruritus.[8]

Therefore, taking into account this problem, the researchers wanted to conduct a research to find out the relationship between IL-6 levels and the incidence of pruritus in patients with chronic kidney disease undergoing regular hemodialysis using the Visual Analog Scale, the Pruritus Scoring System modified by Pauli-Magnus and measurement of IL-6.

## Method

**Study Samples**

The population in this study were all patients with chronic kidney disease who underwent hemodialysis in RSKG Rasyida Medan. Patients with chronic kidney disease must have undergone regular hemodialysis for more than ≥ 3 years, aged ≥ 18 years and have received information and given consent to participate voluntarily in written consent. Patients with primary skin disease and changes in dialysis modalities in the last 3 months before the study were excluded from this study.

**Study Design**

This research is an analytical study with cross-sectional design to assess the relationship between IL-6 levels and the incidence of pruritus in patients with chronic kidney disease who undergo regular hemodialysis. The sampling technique used was consecutive sampling, where all subjects who came in and fulfilled the selection criteria were consecutively included in the study until it meet the required number of samples.

After obtaining approval from the ethics committee, the subjects who met the inclusion and exclusion criteria were given explanation and asked to give informed consent to participate in the study. Data in the form of age, gender, duration of hemodialysis, and history of skin diseases were obtained from medical records or interviews.

Pruritus which is associated with CKD diagnosed based on the criteria(Table 1). Patients were then asked to fill out the Pauli-Magnus questionnaire (Table 2), and laboratory tests to obtain the level of serum IL-6, calcium and phosphate were conducted. Then after the data was collected, data processing and analysis were then conducted.

**Table 1 Diagnostic Criteria of Pruritus Associated with CKD[34]**

1. Pruritus occurred just before the onset of dialysis, or occurred at any time, without evidence of other underlying active disease.
2. More than or equal to three episodes of pruritus within < 2 weeks, which occur several times a day, last for at least several minutes, and interfere with patient's daily life.
3. Pruritus occurs in a regular pattern over a period of 6 months, but is less frequent than mentioned above.

***Table 2. Scoring of Symptoms in Each Questionnaire Parameters***

| Parameters | Score |
|---|---|
| **Degree of Severity** | |
| Minimal itching, without the desire to scratch | 1 |
| Desire to scratch, but without skin damage | 2 |
| Scratching and skin damage | 4 |
| Very disturbing itching | 5 |
| **Location** | |
| Less than 2 locations | 1 |
| 2 locations | 2 |
| More than than 2 locations | 3 |
| **Sleep Disturbance** | |
| Scratching episodes at night causing skin damage | 1-5 |
| Pruritus attack woke the patients from sleep | 2-10 |

**Statistical Analysis**

Univariate analysis is performed to obtain an overview of each variable studied, both the major independent variables, the minor independent variables and the dependent variable.

Bivariate analysis is used to analyze of two variables, namely the dependent variable and the independent variable. To determine the relationship between numeric variables and categorical variables, unpaired t-test was used if it meets the requirements and the Mann-Whitney test if it does not.

## Result

**Research Subjects Characteristic Distribution**

This study was participated by 100 patients who had met the inclusion and exclusion criteria. The study was conducted in April 2018. The majority of respondents were male (60%) with a median age of 57 years. Most of subjects are 55 years of age (53 people or 53%). The majority of subjects had been undergoing hemodialysis for ≤ 5 years (69%) with frequency of 2 times a week (75%) (Table 3). A total of 53 people (53.0%) had taken phosphate-binding drugs containing calcium and 10 people (10.0%) had taken phosphate binding agents without calcium (Table 3). From laboratory tests results, Interleukin-6 (IL-6) levels was 120 mg / dL and out of 100 respondents, 52 of them (52.0%) experienced pruritus. (Table 3)

The median pruritus score was 3 with a median scale of VAS was 1. Pruritus intensity was experienced by many patients, with mild intensity of pruritus experienced by 25 patients (48.07%) and 71.15% of them occurred at night. It was concluded that the mean score of 19.32 for the majority of pruritic events was felt at night with mild intensity with a VAS score of 5. (Table 4)

***Table 3. Characteristics of Research Subjects***

| **Characteristics** | **n = 100** |
|---|---|
| Sex, n (%) | |
| Male | 60 (60,0%) |
| Female | 40 (40,0%) |
| Age, median (min-max), years | 57 (22 – 78) |
| Age, n (%) | |
| <45 years | 18 (18,0%) |
| 45-54 years | 29 (29,0%) |
| ≥55 years | 53 (53,0%) |
| Duration of Hemodialysis, n (%) | |
| ≤ 5 years | 69 (69,0%) |
| >5 years | 31 (31,0%) |
| Frequency of Hemodialysis, n (%) | |
| 2 times a week | 75 (75%) |
| 3 times a week | 25 (25%) |
| Comorbidity, n (%) | |
| Diabetes Mellitus | |
| Yes | 21 (21,0%) |
| None | 79 (79,0%) |
| BMI Classification, n (%) | |
| Normal | 69 (69,0%) |
| Underweight | 2 (2,00%) |
| Overweight | 29 (29,0%) |
| Laboratory Test Result | |
| IL-6 Level, median (min-max), mg/dl | 120 (35,8-665,0) |
| Pruritus Events, n (%) | |
| Yes | 52 (52,0%) |
| No | 48 (48,0%) |

***Table 4. Pruritus Characteristics in Research Respondents***

| **Characteristics (Pauli-Magnus s*coring system*)** | **n = 52** |
|---|---|
| Pruritus Score, Median (Min-Max) | 3 (0-35) |
| VAS, Median (Min- Max) | 1 (0-7) |
| Pruritus Intensity, n (%) | |
| Mild | 25 (48,07%) |
| Moderate | 17 (32,70%) |
| Severe | 10 (19,23%) |
| Pruritus Timing, n(%) | |
| Day | 13 (25,00%) |
| Night | 37 (71,15%) |
| Uncertain | 2 (3,85%) |
| Score*Pruritus Timing, Mean ± SD | |
| Day | 17,23±1,981 |
| Night | 19,32±1,419 |
| VAS*Pruritus Timing, Median (Min- Max) | |
| Day | 4 (2 – 5) |
| Night | 5 (3 – 7) |

Table 5 showed that there were significant differences between the levels of Interleukin-6 and the incidence of pruritus (p= 0.001).

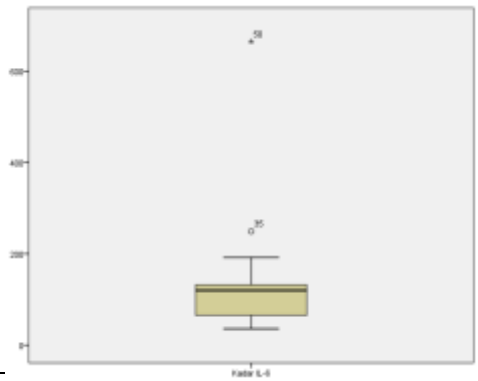
IL-6 levels were associated statistically with the incidence of pruritus (p = 0.001) where subjects with pruritus had more IL-6 levels than those without pruritus (135.77±25.15 mg/dl vs. 77.68±88.13 mg/dL).

***Table 5. Correlation between Risk Factors and Laboratory Tests Results to Pruritus Events***

| **Risk Factors** | **Pruritus Events** | | *p* |
|---|---|---|---|
| | **Yes(n=52)** | **No(n=48)** | |
| Laboratory | | | |
| IL-6 Levels, mg/dl | 135,77±25,15 | 77,68±88,13 | 0,001[c] |

Mann Whiteny

**Picture 1. IL-6 Levels**



## Disscusion

The subjects of this study were dominated by male (60%) with a median age of 57 years. This is in line with the study of Muzasti et al. and DOPPS in patients who underwent HD in 12 countries between 1996-2012 where the prevalence of men was greater than women (59% vs 41%).[9] Women were protected from CKD during reproductive age, furthermore CKD also often occurs in patients with conventional risks such as hypertension, diabetes mellitus, hyperlipidemia, and heart disease, smoking and drinking alcohol which is often found in men.[6]

Subjects were divided into three age groups with the majority of subjects were in age group of ≥55 years, followed by age group of 45-54 years. This is in line with the 2015 IRR that the proportion of the highest number of patients was still in the 45-64 year old category.[5]

**Pauli-Magnus and VAS questionnaires**

The majority of pruritic events with a mean scores of 19.32 were felt at night. The pruritic events were mild intensity with VAS of 5. These results are in line with previous studies stated that pruritus was often found at night (71.15%) with VAS of 5 compared to those happened during the day (25.00) with milder intensity and VAS of 4. Min. et al's study also found that the distribution of patients in each VAS value of > 4 occurred more at night.[10]

In this study, the highest percentage of pruritus intensity was mild intensity (48%). Based on Weiss's research, the prevalence of pruritus was also different based on pruritic intensity experienced by the patients.[9] Mild pruritic intensity occurred in 22 - 52.6% of patients, moderate pruritus in 22.6 - 40% of patients, and severe pruritus in 8 - 40% of patients.[9]

In hemodialysis patients, inflammation plays an important role in pruritus, where a series of inflammatory factors such as interleukin (IL) -31, IL-6, IL-2, and histamine, are reported to be associated with pruritic events.[11] Serum inflammatory marker, including C reactive protein, IL-6 and leukocytes are found to increase in pruritic patients. Interleukin-6 is reported to be most associated with more inflammation than other cytokines and C-reactive protein as it is the central regulator of the inflammatory process.[12,13]IL-6 was statistically significant as a factor influencing the incidence of pruritus, this was similar to results of a study by Shafei et al and Kimmel et al.[6,7] Increased plasma IL-6 levels are caused by oxidative stress, chronic inflammation, and fluid accumulation. Meanwhile, IL-6 is also a non-histaminergic pruritogen.[20] In the process of hemodialysis, blood contact with foreign substances such as bio-compatible elements, contamination of dialysate, acetate and these substance can be a potential source of inflammation. Meanwhile, IL-6 clearance has decreased due to kidney function damage resulting in contribution to the accumulation of IL-6.

However, even though IL-6 had a significant value, the odd ratio value in this study was 1,030 meaning that an increase in IL-6 levels in CKD patients had a risk of 1,030 times greater to have pruritus event. The results of this analysis proved that IL-6 levels were one of the factor that affects the incidence of pruritus even though the risk difference was small. That was due to IL-6 levels are inflammatory cytokines that are not only found in CKD patients undergoing hemodialysis but also is an inflammatory cytokine commonly found in all body tissues that are having inflammation, regeneration, and increased metabolites as humoral body immunity responses.[8,12,20]

## Conclusion

It can be concluded from this study that there is a relationship between Interleukin 6 levels and the incidence of pruritus in chronic kidney disease patients undergoing regular hemodialysis (p = 0.001). The prevalence of pruritus in CKD patients undergoing regular hemodialysis at RSKG RasyidaMedan was 52%. The characteristics of uremic pruritus in CKD patients undergoing hemodialysis were predominantly by male and age > 55 years, had already undergoing hemodialysis for 3-6 years with frequency of 2 times a week. Pruritic events were felt at night with mild intensity and VAS score of 5. The cut-off point value of IL-6 as a predictor of pruritus in patients with chronic kidney disease undergoing regular hemodialysis was 101.550 mg / ml with a sensitivity of 98.1% and specificity of 95.8%.

## Suggestion

We recommend that all chronic kidney disease patients undergoing hemodialysis to be tested for IL-6 levels. In subsequent studies, the authors suggested taking a history of patients' previous treatment, such as anti-histamine or steroids drugs related to pruritus. The author also recommends considering other parameters such as Hemoglobin levels, sleep disturbances, quality of life, blood vessel calcification, and HD adequacy that occur due to IL-6 increase in subsequent studies.

## References

[1] IRR IRR-. 7th Report of Indonesian Renal Registry. In. Indonesia 2014.
[2] IRR IRR-. 8th Report of Indonesian Renal Registry. In. Indonesia 2015.
[3] Mettang, T., Kremer, A.E. Uremic pruritus. Kidney Int. 2015; 87(4) 685 – 691.
[4] Shirazian, S., Aina, O., Park, Y., Chowdhury, N., Leger, K., Hou, L., et al. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. International Journal of Nephrology and Renovascular Disease. 2017: 10(1); 11 – 26.
[5] Pisoni, R.L., Wikstrom, B., Elder, S.J., Akizawa, T., Asano, Y., Keen, M.L., et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2006; 21: 3495 – 3505.
[6] Aramwit, P., Supasyndh, O. Uremic Pruritus; Its Prevalence, Pathophysiology and Management. In: Suzuki, H. Update in Hemodialysis. Croatia: InTech; 2015, 19 – 41.
[7] Filho, R.P., Lindholm, B., Axelsson, J., Stenvinkel, P. Update on interleukin-6 and its role in chronic renal failure. Nephrol Dial Transplant. 2003; 18: 1042 – 1045.
[8] Kimmel, M., Alscher, D.M., Dunst, R., Braun, N., Machleidt, C., Kiefer, T., et al. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. Nephrol Dial Transplant. 2006; 21: 749 – 755.
[9] Muzasti RA, Lubis HR. Association of phase angle on bioelectrical impedance analysis and dyalisis frequency with survival of chronic hemodialysis patients. Earth and environmental science. 2018 : 125 (1)
[10] Min, J.W., Kim, S.H., Young, O.K., Jin, D.C., Song, H.C., Choi, E.J., et al. Comparison of uremic pruritus between patients undergoing hemodialysis and peritoneal dialysis. Kidney Res ClinPract. 2016; 35: 107e113.
[11] Wu, H.Y., Peng, Y.S., Chen, H.Y., Tsai W.C., Yang, J.Y., Hsu, S.P., et al. A Comparison of Uremic Pruritus in Patients Receiving Peritoneal Dialysis and Hemodialysis. Medicine. 2016; 95(9): 1 – 6.
[12] Shafei, N.K., Nour, A. Observations on the Association of Serum histamine, Interleukins and Other Serum Biochemical Values with Severity of Pruritus in Chronic Hemodialysis Patients. NanomedNanotechnol. 2016; 7(1): 1 – 6.
[13] Atmojo, D.S. PrinsipdanIndikasiHemodialisis. PertemuanIlmiahTahunanIlmuPenyakitDalam, 2000, 3(1) : 1 – 8.
[14] Asicioglu, E., et al. Uremic Pruritus: Still Itching. Turkish Nephrology, Dialysis and Transplantation Journal. 2011; 20 (1): 7 – 13.
[15] Magnus, C.P., Mikus, G., Alscher, D.M., Kirschner, T., Nagel, W., Gugeler, N., et al. Naltrexone Does Not Relieve Uremic Pruritus: Results of a Randomized, Double-Blind, Placebo-Controlled Crossover Study. J Am SocNephrol. 2000; 11: 514 – 519.
[16] Santoro, A., Mancini, E. Is hemodiafiltration the technical solution to chronic inflammation affecting hemodialysis patients? Kidney International. 2014; 86: 235 – 237.
[17] Gatmiri SM, MahdaviMazdeh M, parezeski Tm, Abbasi m. Uremic Pruritus And Serum Phosphorus level. Acta Med Iran 2013.
[18] Suzuki, H., Omata, H., Kumagai, H. Recent Advances in Treatment for Uremic Pruritus. Open Journal of Nephrology. 2015; 5(1): 1 – 13.
[19] Akhyani M, Ganji M-R, Samadi N, Khamesan B, Daneshpazhooh M. Pruritus in hemodialysis patients. BMC Dermatology. 2005.
[20] Frank Brennan. The pathophysiology of pruritus – A review for clinicians. Progress in Palliative Care. 2016; 24(3): 133 – 146.